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ACUTE PULMONARY EMPHYSEMA OBSERVED DURING THE EPIDEMIC OF INFLUENZAL PNEUMONIA AT CAMP HANCOCK, GEORGIA. By ROBERT C. TORREY, Captain, M. C., U. S. A., and LAWRENCE C. CROSBY, Captain, M. C., U. S. A. . . . 170

PRIMARY CARCINOMA OF THE THIRD PORTION OF THE DUODENUM. By GEORGE DOUGLAS HEAD, M.D. . . . 182

REPORT ON THE EXAMINATION AND TREATMENT OF SOLDIERS INFECTED WITH HOOKWORM AT CAMP BEAUREGARD, LA., MARCH 1 TO SEPTEMBER 1, 1918. By DONALD J. FRICK, Major, M. C., U. S. A. . . . 189

GRANULAR TUBERCULOUS CONJUNCTIVITIS TREATED BY INSTALLATIONS OF TUBERCULIN. By ROBERT C. PATERSON, M.D. . . . 198

STUDY OF AN UNUSUAL GLYCOSURIA. By LOUIS [illegible]STROTH, M.D. . . . 201

THE GRAHAM-STEELL MURMUR IN MITRAL STENOSIS. By EDWARD H. GOODMAN, Major, M. C., U. S. A. . . . 206

ON THE USE OF A BINOCULAR LOUPE FOR THE EXAMINATION OF THE FUNCTIONAL TROUBLES OF THE PUPIL. By Dr. EMIL BERGER . . . 208

EPIDEMIC CEREBROSPINAL MENINGITIS AT CAMP BEAUREGARD, LA. By ADRIAN A. LANDRY, Captain, M. C., and WILLIAM H. HAMLEY, Lieutenant, M. C. . . . 210

INFLUENZA-PNEUMONIA CASES SHOWING GAS IN FASCIAL TISSUES. By ELBERT CLARK, Ph.D., M.D., Major, M. C., U. S. A., and MARTIN J. SYNNOTT, A.M., M.D., Major, M. C., U. S. A. . . . 219

RENAL DIABETES. By CAMERON VERNON BAILEY, M.D. . . . 221

MULTIPLE ENDOTHELIOMA OF THE SKIN. By FRED WISE, M.D. . . . 236

CLINICAL RESULTS IN TWO HUNDRED TRANSFUSIONS OF CITRATED BLOOD. By RICHARD LEWISOHN, M.D., F.A.C.S. . . . 253

A REPORT OF THE PATHOLOGICAL CHANGES OF THE BRAIN IN 162 CASES OF PARESIS. By THOMAS B. CHRISTIAN, A.M., M.D. . . . 271

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CONTENTS

ORIGINAL ARTICLES

Clinical Studies in Cutaneous Aspects of Tuberculosis. I. "Tuberculous" Purpura, Erythema Multiforme and Erythema Nodosum . 157

By JOHN H. STOKES, M.D., Head of the Section on Dermatology and Syphilology, Mayo Clinic, Rochester, Minnesota.

Acute Pulmonary Emphysema Observed during the Epidemic of Influenzal Pneumonia at Camp Hancock, Georgia 170

By ROBERT G. TORREY, Captain, M. C., U. S. Army, Philadelphia, Pa., and LAWRENCE C. GROSH, Captain, M. C., U. S. Army, Toledo, Ohio, Chief and Assistant Chief of Medical Service, Base Hospital, Camp Hancock, Ga.

Primary Carcinoma of the Third Portion of the Duodenum 182

By GEORGE DOUGLAS HEAD, M.D., Minneapolis, Minnesota.

Report on the Examination and Treatment of Soldiers Infected with Hookworm at Camp Beauregard, La., March 1 to September 1, 1918 189

By DONALD J. FRICK, Major, M. C., U. S. Army.

Granular Tuberculous Conjunctivitis Treated by Instillations of Tuberculin 198

By ROBERT C. PATERSON, M.D., Saranac Lake, N. Y.

Study of an Unusual Glycosuria 201

By LOVELL LANGSTROTH, M.D., San Francisco, California.

The Graham-Steell Murmur in Mitral Stenosis 206

By EDWARD H. GOODMAN, Major, M. C., U. S. Army, Special Board for Cardiovascular Examinations, Camp Jackson, S. C.

On the Use of a Binocular Loupe for the Examination of the Functional Troubles of the Pupil 208

By EMIL BERGER, M.D., Corresponding Member of the Royal Academy of Medicine of Belgium.

Epidemic Cerebrospinal Meningitis at Camp Beauregard, La. 210

By ADRIAN A. LANDRY, Captain, M. C., Plaquemine, La., and WILLIAM H. HAMLEY, Lieutenant, M. C., Lake Providence, La.

(Contents continued on page 8)

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CONTENTS (*Continued*)

Influenza-Pneumonia Cases Showing Gas in Fascial Tissues . . . 219
By Elbert Clark, Ph.D., M.D., Major, M. C., U. S. Army, Chief of Laboratory Service, Chicago, and Martin J. Synnott, A.M., M.D., Major, M. C., U. S. Army, Chief of Medical Service, Montclair, N. J.

Renal Diabetes 221
By Cameron Vernon Bailey, M.D., Assistant Professor of Medicine, New York Post-Graduate Medical School and Hospital; Captain in the Canadian Army Medical Corps.

Multiple Endothelioma of the Skin 236
By Fred Wise, M.D., Instructor in Dermatology and Syphilology, Columbia University, College of Physicians and Surgeons; Chief of Clinic, Department of Dermatology and Syphilology, Vanderbilt Clinic and Mt. Sinai Hospital Dispensary, New York.

Clinical Results in Two Hundred Transfusions of Citrated Blood . . 253
By Richard Lewisohn, M.D., F.A.C.S., New York.

A Report of the Pathological Changes of the Brain in 162 Cases of Paresis 271
By Thomas B. Christian, A.M., M.D., Pathologist, State Hospital for Insane, Norristown, Pa.

REVIEWS

Medical War Manual No. 7. Military Surgery of the Zone of the Advance. By George de Tarnowsky, Major, M. C., U. S. R. . . 276
Bipp Treatment of War Wounds. By Rutherford Morison 276
"Trench Fever." Report of American Red Cross Research Committee 277
War Wounds of the Lung. By Pierre Duval 280
Surgical Clinics of Chicago. By Numerous Authors 281
Manual of Splints and Appliances for the Medical Department of the United States Army. By Lieutenant-Colonel W. L. Keller, M. C.; Major R. B. Osgood, M. R. C.; Major A. Lambert, M. R. C.; Major J. A. Blake, M. R. C.; Captain W. S. Baer, M. R. C., and N. Allison, M. R. C. 281
Amputation Stumps: Their Care and After-treatment. By G. Martin Huggins 282
Essentials of Materia Medica and Therapeutics (Lippincott's Nursing Manuals). By John Foote, M.D. 282
Medical Clinics of North America 282
Proteomorphic Theory and the New Medicine. By Henry Smith Williams, B.Sc., M.D., LL.D. 283
International Medical Annual. A Year-book of Treatment and Practitioners' Index 284
Aids to Rational Therapeutics. By Ralph Winnington Leftwich, M.R.C.S., Eng. 284
Genito-urinary Diseases and Syphilis. By Henry H. Morton, M.D. . . 285
The Prevention of Venereal Diseases. By Otto May, A.M. (Cantab.), M.R.C.P. 286

(*Contents continued on page 10*)

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Contributions to the Physiology of the Stomach; Studies on the Control of Hunger by Drugs 288

OBSTETRICS

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Rupture of the Uterus through the Cesarean Section Scar 289
Delivery by Abdominal Section 290
Can the Frequency of Some Obstetrical Operations be Diminished? . . 291
Sensitized Vaccines in the Prophylaxis and Treatment of Infections . . 293

GYNECOLOGY

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Estimate of Radium Therapy in Uterine Cancer 294
Biological and Clinical Evidence of the Therapeutic Value of Radium and Roentgen Rays in Cancer 295
Treatment of Fibroid Tumors of the Uterus with Radium 295
Radium in Gynecology 296

(*Contents continued on page 12*)

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Acute Respiratory Diseases Among Troops, with Special Reference to Empyema 297
Experimental Chemical Pneumonia 298
Studies of Bacteriemias in the Agonal Period 298
Acid Production by Bacteria 299
Observations on the Presence of Meningococcus in the Blood 299
Relationship of the Leukocyte Count and Bone-marrow Changes in Acute Lobar Pneumonia 300
Experimental Carcinomata of Animals and Their Relation to True Malignant Tumors 300
Importance of the Lymphocyte in Cancer Immunity 301
Spirillosis 302

(*Contents continued on page 14*)

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Physiological Effects of Siliceous Dust on the Miners of the Joplin District 302
Report on Attempts to Cultivate the Virus of Epidemic Poliomyelitis . 303
Color Blindness: Its Relation to Other Ocular Conditions and the Bearing on Public Health of Tests for Color-sense Acuity . . . 303
Transmission of Poliomyelitis 304
Clinical and Epidemiological Studies on Epidemic Meningitis 306
Diagnosis of Epidemic Meningitis and the Control of its Treatment by Rapid Bacteriologic and Serologic Methods 306
Comparison of Methods for the Examination of Water at Filtration Plants 306
Further Studies on Bacterium Abortus and Related Bacteria 307
Streptothrix (Nocardia) Infection of Cows' Udders 307
Prevailing Pandemic of Influenza 308
Rat and Poliomyelitis 308
Further Study of Experimental Parotitis 309
Spirocheta Hebdomadis, the Causative Agent of Seven-day Fever . . 309
Report on Antimeningitis Vaccination and Observations on Agglutinins in the Blood of Chronic Meningococcus Carriers 309
Action of the Extreme Ultraviolet of Tropical Sunlight on the Complementing Power of Serum 310
Protective Therapy for Varicella and a Consideration of its Pathogenesis 310
Scurvy 310
Psychiatric Material in the Naval Prison at Portsmouth, N. H. . . . 311
Etiology of Epidemic Poliomyelitis 312
Experimental Test of Nuzum's Antipoliomyelitic Serum 312

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ORIGINAL ARTICLES

CLINICAL STUDIES IN CUTANEOUS ASPECTS OF TUBERCULOSIS.

I. "TUBERCULOUS" PURPURA, ERYTHEMA MULTIFORME AND ERYTHEMA NODOSUM.

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The tendency of recent advances in the study of the etiology of dermatoses has been, increasingly, to show that many supposed clinical entities, so styled on purely morphological grounds, have a multiple etiology. One of the conditions undergoing such etiological revision is the erythema group, including the clinical entities of erythema multiforme and erythema nodosum. The work of revising our outlook on erythema multiforme, purpura and urticaria was well begun by Osler in 1895. Erythema nodosum is of particular interest because on its border lie erythema induratum and the group of dermatoses designated after Darier as "tuberculids," whose intimate relation to tuberculosis is now generally accepted. Erythema nodosum, on the basis of the experimental evidence cited herein, is in a fair way to be at least partially allied to this group, and it awaits only a sufficient body of clinical evidence and some corroborative work to establish its connection. The fact that the majority of American dermatological texts have not yet given this phase of the matter the attention it deserves, probably accounts for the seeming unfamiliarity of internists, surgeons and general diagnosticians, with the very great diagnostic and prognostic significance of purpura, erythema multiforme, erythema nodosum and the tuberculids. My

own interest in the relation of this group of dermatoses to tuberculosis was aroused by the death of a patient having the miliary type of the disease, following an onset in the form of purpura rheumatica and succeeded by erythema multiforme.

The material here presented forms part of a series of approximately forty cases of erythema nodosum, erythema multiforme with purpura, erythema induratum and the various types of papulonecrotic tuberculids seen on the service of the Section on Dermatology of the Mayo Clinic during the past two years (1916–1917). The material is presented in a separate communication in the hope of emphasizing the possibility of this form of onset of tuberculosis and of arousing the attention of diagnosticians and internists in this country to its importance from the standpoint of diagnosis and treatment.

The literature on the subject of the association of erythema nodosum with tuberculosis was ably reviewed in 1914 by Foerster, who reported 2 cases of his own. A large proportion of the cases recorded elsewhere were in children. Since Foerster's summary, articles by Nicola (who also cites De Blasi) and Jaquerod have appeared: the former reported 6 and the latter 2 cases. Cecicas considers the good effect of heliotherapy an evidence of the tuberculous origin of the disease. The French investigators, including Chauffard, Sezary, Marfan, Brian and Landouzy, have been especially active in the study of erythema nodosum and have been vigorous proponents of the theory of tuberculous etiology. Landouzy, for example, by his successful inoculation of tuberculosis into guinea-pigs by material from the lesions of erythema nodosum, has supplied the best experimental evidence of the tuberculous nature of certain forms of the disease. Brian has accomplished a similar result. Hildebrandt, in 1907, reported inoculation from the blood at the height of the attack, but interprets his results with reservations.

One of the very interesting features of the etiological developments concerning erythema nodosum is the demonstration by Rosenow in 1915 of a polymorphous gram-negative diphtheroid as the cause of the condition. This organism, whose infection-atrium is apparently the tonsils and pus pockets about the teeth, gives rise especially to the more acute types of the disease. The pathology of erythema nodosum, however, is such that it seems a rash assumption to attribute the changes to a single type of organism. There would appear to be no reason why embolic infarction or thrombosis of terminal vessels in the skin of the extremities, and varying grades of exudation and inflammatory reaction about the affected vessels, could not be produced by living tubercle bacilli in a hypersensitive individual, as suggested by the studies of Rist and Rolland, or by the dead bodies or the "toxins" of the same organism, as suggested by the experiments of Chauffard. While with a larger experience we may

come to recognize clinical differences between erythema nodosum produced by the tubercle bacillus or its products and that produced by the Rosenow diphtheroid, or perhaps by streptococci, the assumption that the pathological differences between the various types will be striking and pathognomonic is in the present uncertain state of knowledge gratuitous. It seems not unlikely that the clinician who ascribes too high a degree of etiological specificity to a condition such as erythema nodosum will fail to recognize many important relations of the picture and will overlook other etiological possibilities which may be of the greatest import to the particular case.

The 10 cases which form the subject of this report in contrast with a number of those reported in the literature occurred in adults. The youngest patient was sixteen years of age, the oldest forty-three; the majority over twenty-five.

Case 1 (A–202732), a girl, aged twenty-four years, an indoor worker, gave a negative family and personal history. The patient complained chiefly of a cough and an eruption on the legs. For four weeks she had had a slight sore-throat but no tonsillitis. Two days after the onset of the pharyngitis, erythematous nodes, varying from 2.5 to 5 cm. in diameter and from eight to ten in number, appeared over the pretibial region. In color, tenderness, induration and tenseness the lesions were typically those of erythema nodosum; they improved under salicylates and rest. The patient's temperature subsided in two weeks from onset. She had lost 21 pounds in weight during the four weeks of the attack. She coughed, with some expectoration, but a negative sputum examination; no night-sweats or hemoptysis. Examination of the chest indicated signs of a doubtful character over the right lower lobe, with suggestive but not pathognomonic findings in the roentgenogram. The diagnosis was regarded as indeterminate, and the patient was placed at once on antituberculous hygiene. She improved, recovered weight and remained well, although she did not work for six months. In February she had grippe, which lasted more than two months, with loss of strength, weight and appetite. The patient was reëxamined in June, nearly a year after the attack of erythema nodosum. At this time breath sounds were prolonged over the right lobe and the whispered sounds were markedly increased. No evidence of active tuberculosis could be recognized in the roentgenogram. She had no temperature, hemoptysis, increased pulse, nervousness or sweats. Antituberculous hygiene was continued, with the patient under observation.

This case from a dermatological point of view was a classical erythema nodosum in every morphological detail. No focus of infection in the form of bad tonsils or infected or abscessed teeth was apparent. The question as to whether or not the patient is tuberculous is, of course, *sub judice*, but should be viewed in the light of the following case.

CASE 2 (A–49238), a male, aged thirty-eight years, has been under observation in the Clinic for seven years. In 1911 he was referred for treatment by his home physician because of shifting pains, stiffness and purpura of ten days' duration. While the patient's physician conceded that the purpura suggested rheumatism, he personally was inclined to suspect tuberculosis of which, in miliary form, the patient's sister had died. Six months before the onset of symptoms the patient had been in bed with "typhoid" for twelve days. At the time of examination purpuric lesions were present on the shins, shoulders and chest. A rise in temperature was reported; he had lost appetite but no weight. Evanescent rales were heard posteriorly over the left lung. Enlarged glands in the left axilla and cervical regions were noted and the roentgenogram showed beginning tuberculosis of both apices; the sputum, however, was negative. In 1914 the patient was again seen for a brief period, but the tuberculous process was then quiescent. In 1918, seven years after the onset of the purpura and three years after the patient was last observed, my assistant was called to see him during an attack of erythema nodosum, which I had the opportunity to observe as it was subsiding. At this time numerous deep subcutaneous erythematous nodes over the tibiæ and many less erythematous, smaller and paler shotty indurations, were found. The chain of lymphatics along the left pectoralis major and the axillary and mammary nodes were enlarged and, in some instances, caseous and calcified. Subsequent resection of these glands at operation established the pathological diagnosis of tuberculosis.

This case differed from the conventional picture of erythema nodosum only in the greater pallor and smaller size of many of the nodules, in the absence of the ecchymotic color changes and in the generally lesser activity of the process. At its height, however, it was quite within the usual limits of variation of the clinical picture of erythema nodosum. The purpura, with rheumatoid pains in the early years of the disease observed in this patient, is one of the features common to other cases to be cited hereinafter.

The following case is illustrative of the manner in which a purpuric onset and a tuberculid may precede, by months or years, the gross clinical evidence of active tuberculosis.

CASE 3 (A–154673), a man, aged thirty-one years, a tailor, first came to the Clinic in 1916 because of a scrotal hernia, which was operated on, with good results. At that time the patient gave a history the significance of which was not appreciated until later. A year before his first examination he had an attack of grippe followed by a purpuric eruption. The macules were from a pinhead to a dime in size; some of them had "blistered" and left scars on the extremities. Apart from a small colloid goitre, a hernia and a lichenified scrotum his examination was negative. No radiographic examination was considered necessary in view of the absence of

symptoms. One year and a half after this examination and the operation for hernia the patient returned, giving a history of "sciatica," and of an abscess that had drained through the buttock, and had left a persistent sinus. Bismuth injection demonstrated a draining sacro-iliac abscess. The patient was then seen by a dermatological consultant because of the scars on the legs, which were typically those of a tuberculid, although there were then no active lesions. The operation on the sinus disclosed a tuberculous process, probably originating in the lumbar or sacral spine.

If a dermatologist had seen the purpura and the tuberculid at the first examination two years previously and appreciated its significance a more thorough search might have disclosed the focus.

Case 4 (A–157847), a woman, aged thirty-three years, a clerical worker, came to the Clinic, in 1916, with a history of severe anemia two years before, from which she had recovered under treatment with iron. A year later a lump, not, however, preceded by any sore-throat, appeared on the right side of the neck. In fact, the patient had never had sore-throat or tonsillitis. Abruptly, two months after coming to the Clinic, and nearly two years after the appearance of the glands, the legs swelled markedly without apparent cause and were covered with raised, red lumps. The patient had a temperature of 103° and was confined to bed for two weeks; the temperature subsided but the edema persisted. Examination disclosed a pale, rather fat girl, with numerous erythematous nodules and hyperemic plaques on both legs and arms. The plaques in particular were more suggestive of erythema multiforme than of the conventional erythema nodosum. Their comparative pallor may have been due to the anemia. None of the lesions had shown any tendency to ulceration. The temperature was normal; hemoglobin, 40 per cent.; a marked glandular enlargement on the right side of the neck was shown, by subsequent excision for diagnosis, to be tuberculous. The radiograph of the chest showed healed pulmonary tuberculosis, involving both apices. The tonsils were markedly septic. After the removal of the tuberculous glands a tonsillectomy was performed. This, however, did not prevent the continued appearance of nodular lesions on the legs. Although these did not at any time become ulcerative, the picture approached more and more nearly that of erythema induratum of Bazin, for which we treated the patient a year later.

The typical onset of erythema nodosum in this case, two years after the appearance of the glands, was combined with the appearance of lesions suggestive of erythema multiforme. The nodose lesions persisted and recurred, constituting a chronic erythema nodosum, so to speak, even after tonsillectomy had removed a possible atrium of infection for diphtheroid and other organisms and a block dissection had removed a portion of the tuberculous

focus. There was nothing to suggest a dental source of infection. That the tuberculous focus which was the probable source and perpetuator of the process had not been done away with, is shown by the subsequent re-operation for recurrences in the glands. The following is a case of somewhat similar type:

CASE 5 (A–22802), a girl, aged twenty-three years, a rancher, three years before coming to the Clinic, had sustained surgical removal of cervical glands and tonsillectomy, at which time a pathological diagnosis of tuberculous adenitis was made. The tuberculous process had extended to new glands in spite of tuberculin and an outdoor regime. For two weeks before her examination in the Clinic she had felt tired and her legs had ached, following which an eruption of "lumps" appeared abruptly below the knees on the posterior surface of the legs. These were beginning to involute spontaneously. On examination bluish moderately infiltrated plaques were recognized on the calves of the legs; these disappeared under appropriate treatment. The roentgenogram of the chest was negative. The tuberculous nature of the adenitis had been established by the previous pathological examination and there was a visible and palpable recurrence.

The onset in this case suggests a mild erythema nodosum. In its distribution on the calves and in the relative indolence of the lesions it approached more nearly the type of erythema induratum and should be compared with the preceding case and the last case in the series. The whole picture developed three years after the removal of a tonsillar focus, but while the tuberculous focus was still active. The next case, while perforce left indeterminate, illustrates very well the type of erythema nodosum onset which may eventuate in an active tuberculosis such as that suspected in Case 1 and identified in Case 2.

CASE 6 (A–188556), a man, aged forty-four years, reported at the Clinic with the statement that three weeks before he had caught a common cold. He felt weak since the onset of the infection and had had a cough and expectoration for two weeks. There were some aching and edema of the legs. The past respiratory history was not significant. On examination a very marked right cervical adenopathy was found. The patient's afternoon temperature was 100°. The extensor surfaces of the arms and legs were studded with deep-seated nodules varying from 0.5 to 1.5 cm. in diameter and from a yellowish pink to a deep violaceous color. Over the anterior tibial region there were numerous larger lesions, which were, on the whole, however, somewhat smaller and less ecchymotic than those of a well-developed erythema nodosum, and showed signs of early involution. The lesions about the wrists were of the erythema multiforme type and few in number. A few papulopustules had appeared. Examination of the thorax disclosed prolonged breath sounds and increased fremitus over the right apex. The radio-

graphic examination of the chest, a Wassermann test and the blood culture were all negative.

This case is especially instructive because, in addition to presumptive signs of tuberculosis in the form of localized lymphadenitis, the cutaneous manifestations included erythema multiforme lesions about the wrists, erythema nodosum over the tibiæ and a few pustular lesions suggesting the acute generalized miliary tuberculosis of the skin seen in children and more rarely in adults. The lung signs were inconclusive but suggestive.

The next case illustrates how the appearance of an erythema multiforme as a manifestation of obscure tuberculosis may be followed by the development of a tuberculid. The history aligns itself with that of Case 3 (A–154673), who gave a history of a purpura followed by a papulonecrotic tuberculid, as an illustration of the importance of the individual history of cutaneous manifestations in a proper interpretation of the relation of purpura and erythema multiforme to tuberculosis.

Case 7 (A–224920), a young girl, aged sixteen years, gave an extraordinary family history, on the mother's side, of tuberculosis in both direct and collateral lines. The mother herself had been examined in the Clinic, although not by a dermatologist, and the presence of "yellowish-brown stain-like spots" on the legs had been noted. A diagnosis of anemia and septic teeth was made in the mother's case; the daughter was referred to us on a provisional diagnosis of Raynaud's disease because of the cyanosis of her hands and the history of attacks of "blisters" on the fingers. Her father described to us a fairly typical though abortive attack of erythema multiforme, involving the hands and wrists, which had preceded the present trouble by about four years. The description of the condition at the time of the examination was that of a vernal attack of folliclis, of which the scars were distinctly visible on the dorsal aspects of the terminal phalanges. Similar lesions had developed on the toes. The general examination disclosed the presence of rales and increased dulness over the right lung apex, although the examiner was not in the least under the influence of a preconceived notion about the case, since he had made a diagnosis of Raynaud's disease. Although the roentgenogram of the chest was negative, we advised, in view of the history and the tuberculid scars, that an antituberculous regimen be adopted. The tonsils had been removed for recurrent tonsillitis four years before the onset of the folliclis.

The last case of the series illustrates the association of purpura with a typical tuberculid, erythema induratum and the prominence of arthritic symptoms, which might well lead to misinterpretation of the process in its earlier stages as a septic or rheumatic infection.

Case 8 (A–233765), a very large, florid woman, aged thirty years, decidedly overweight, whose father had died of empyema and lung

trouble, was referred to my service for a very typical erythema induratum with papulonecrotic lesions and ulceration involving the calves of both legs. On examination it was found that the patient had many cutaneous nodes scattered over both extremities, with purpuric lesions over the arms, trunk and chest. She had an arthralgia and myalgia of the right shoulder which prevented her from raising her arm to her head, and reported that six years before she had had "rheumatic fever." The tuberculid antedated the "rheumatism" by eight years. The teeth were negative, tonsils only slightly septic, roentgenogram of the chest negative and no glands were identified. The tuberculid responded rapidly to treatment, but the nodules in the upper extremities continued to recur.

This case represents a type of patient not unfamiliar to both dermatologist and internist in which a florid and rather obese exterior conceals a focus of tuberculosis which at times cannot be identified. The case is included with the series to illustrate the association of purpura, with a cutaneous lesion whose tuberculous character is now generally conceded.

Before summarizing the lessons to be drawn from such a series of cases I shall further illustrate the diagnostic problems presented by erythema nodosum from the standpoint of tuberculosis by two examples drawn from clinically typical erythema nodosum, diagnosed as such in my records, but with the reservation that observation of their cases shall be continued for some time.

Case 9 (A–194220), a woman, aged thirty-two years, indoor worker, after being "under the weather" for some time, presented herself looking decidedly ill. She complained of a slight sore-throat, arthritis of the knees and ankles and of having numerous large, deep infiltrated nodose lesions of a dark reddish to purplish color in the pretibial region and on the front of the thighs. Typical lesions of erythema multiforme were found on the backs of the hands and on the neck. There was nothing in the history to lead one to suspect tuberculosis. The tonsils were markedly septic and several alveolar abscesses were demonstrated by the radiogram. The patient showed, however, physical signs of a slight right-sided pleurisy at the base, and the radiogram was suspicious. The erythema nodosum disappeared entirely on salicylates, after which the pyogenic foci were removed and she improved rapidly, all pulmonary signs disappearing to such an extent that a contemplated sanitarium regime was given up.

There are no signs of a tuberculous process in this case four months after the attack of erythema nodosum, but an experience with erythema nodosum of the type illustrated by the foregoing cases would lead one to insist on further observation. Petroff, it will be recalled, has directed attention to the effect of intercurrent infection in temporarily lighting up tuberculous foci to the point at which they can be recognized for a brief time, only to disappear again with the sub-

sidence of the incidental infection. Abt, in 1907, also suggested that it was the function of erythema nodosum to prepare the way for tuberculosis, a conception which loses none of its plausibility in this type of case by the further belief that there may be a true tuberculous erythema nodosum represented by the first eight cases of this series as well.

CASE 10 (A–235299), a housewife, aged twenty-seven years, presented the lesions of erythema nodosum over the front of the thighs and pretibial region, many of them large and tumid, with marked arthritic onset. The patient had lost 15 pounds in weight during eight weeks of the acute process before she was first seen. She exhibited a definite hyperpigmentation overlying a pasty pallor. A history of tonsillitis some years before was obtained. The lesions were not and had not been painful, although in all other particulars they conformed to the strict erythema nodosum type, even to the ecchymotic changes. The tonsils were not septic and the radiogram of the teeth was negative. The patient had a unilateral phlyctenular conjunctivitis, not especially suggestive of tuberculosis. On the other hand, the radiogram of the thorax showed a markedly thickened right hilus, indicating enlarged glands.

Although the patient made an almost miraculous recovery under salicylates it would be folly to release her from further observation for the settlement of the question of concealed tuberculosis. Had her symptoms been accepted at their face value no investigation of this question would have been made and the condition would have been regarded as "rheumatic."

DISCUSSION AND SUMMARY. The series here presented is too small for a satisfactory statistical summary, and for that reason will be incorporated for interpretation in another paper with the group of tuberculids of which it forms a part. Briefly, however, it is of interest to note that the clinical picture of tuberculous purpura, tuberculous erythema multiforme and tuberculous erythema nodosum is made up of objective rather than subjective symptoms. Estimated by a rigorous standard, 4 of the first 8 cases were positively demonstrated as tuberculous, and the remaining 4 were of a highly suspicious nature if not absolutely definite; 2 additional cases of erythema nodosum, morphologically conforming to the conventional or rheumatic type, were also suspected of being tuberculosis and are under observation. Of the 8 original cases the tuberculous focus in 4 was identified by pathological examination; 2 were positive and 1 indeterminate in the roentgenogram of the chest; 4 showed physical signs in the lung and 1 was indeterminate, and 4 had visible and palpable adenopathy. No evidence of syphilis could be identified in any of the 10 cases; 2 of the patients had tuberculids of the papulonecrotic and erythema induratum type, and 1 of them had folliclis, a tuberculid of the fingers; 3 presented purpuric lesions, 3 had lesions of the erythema multiforme type

and 6 had nodular lesions of the type met with in erythema nodosum, though of varying grades of acuteness and severity. In 2 of the cases of nodular erythema the onset was that of erythema nodosum and the localization approached that of erythema induratum. In 1 of these cases the nodose lesions were associated with a typical erythema induratum with ulceration.

Of the 8 cases in the original group 3 presented a family history of tuberculosis and in 1 it was strongly suspected though not absolutely definite. That the onset of the cutaneous manifestations is not necessarily coincident with the onset of the tuberculous infection is apparent from the fact that the shortest probable duration of the active process varied in the cases reported from five months to eight years. The usual points of inquiry in a history of tuberculosis, as to night-sweats, hemoptysis, etc., yielded little information. Two patients only had cough, none had night-sweats and none showed blood in the sputum. The sputum of the 2 who coughed was negative. On the other hand 5 of the 7 of whom data were available showed increased temperatures during the active process, varying from 99° to 103°. Only 1 presented a significant anemia (40 per cent. hemoglobin). The absence of leukocytosis or the presence of a slight leukopenia even in the febrile cases was notable and in keeping with the suspected tuberculous etiology. The counts varied from 5000 to 9600.

The habitus and general condition of the patients afforded little clue to the nature of the disturbance, since the septic cases were indistinguishable from the tuberculous. Loss of weight does not seem to have been a conspicuous feature, although 3 out of the 10 cases discussed showed sharp drops, from 8 to 21 pounds in from five to eight weeks.

The consideration of the possibility of a septic focus in these cases was of interest. In 1 of the patients the tonsils did not seem involved, in 2 they were mildly septic but not markedly affected; a fourth with markedly infected tonsils had them removed without appreciable effect on the process and 2 developed their first attack, 1 of erythema nodosum and the other of folliclis three and four years after the removal of the tonsils. While gross examination for an alveolar or gingival focus was negative throughout the series of 10 cases, in 1 suspected case the patient had an alveolar abscess demonstrable by the radiogram; 2 cases were negative. Radiograms of the teeth were not taken in the remainder. The secondary focus of pyogenic or diphtheroid infection seems to be a negligible quantity in this group, although its importance is much more apparent in a review of the entire series of tuberculids; 4 in 10 had symptoms of a rheumatic character, in the form of myalgia, arthralgia and neuritis. The modes of onset in the 10 cases were slight sore-throat in 2, cold and grippe in 2, typhoid, so-called, in 1 and by indefinite non-localizing symptoms or the typical abrupt onset of

erythema nodosum in 5. The part played by the respiratory atrium is much more apparent in the larger series.

Dermatologically the differentiation of tuberculous from streptococcal or diphtheroid erythema nodosum can scarcely be worked out on so small a group of cases. A tentative personal view of the matter is as follows: While the two conditions are at times indistinguishable from each other on the score of acuteness, localization and course, and this fact cannot be too forcibly emphasized, the following table embodies the main points of difference as the writer has seen them:

Streptococcal Erythema Nodosum.	Tuberculous Erythema Nodosum.
Nodes larger, more edematous, and brawny, more tense, and hemorrhagic. May reach the size of a small palm.	Nodes smaller, less marked peripheral reaction, hemorrhagic changes less marked. In their place may be purplish lividity, but usually only a well-developed erythema.
Greater involvement of the superficial tissues.	Nodules more circumscribed and deeper.
Distribution more apt to be over the front of the lower extremities, especially below the knees and over the front of the thigh; also around the larger joints.	May appear on either front or back of the leg, but tends to localize posteriorly. May appear in smaller numbers or in crops or groups, or one or two on the upper extremities. May appear on the feet.
Color changes, more marked than in the tuberculous type. The brown element especially marked. Behaves typically like a bruise.	The nodule is paler at the onset, and progresses from pink to a livid purple or bluish tinge. If it persists (as erythema induratum) it remains bluish, softens and may show a bullous surface or undergo necrotic sloughing. The nodules may present only a mild erythema which subsides, leaving no color changes or only a faint yellow stain, or there may be colorless ones among the erythematous nodes, suggesting Wende's nodular tuberculosis of the hypoderm.
Symptoms in general more severe, progress more rapid, whole process more acute, tendency to self-limited course.	Process more indolent, lesions less tender or even painless, more persistent, may last months or longer, especially if there is little inflammatory reaction. Of material assistance in diagnosis is the concomitant occurrence of an indubitable tuberculid, such as follicilis, or the papulonecrotic types of lesions or their scars.

Our experience with the diagnostic problems involved in erythema nodosum has led us to formulate for ourselves a series of procedures which should be carried out in all cases in order to establish or eliminate the possibility of a tuberculous infection. First of all, a painstaking search of family and past history for evidence of tuberculosis should be made even though the case seems typically of the rheumatoid type. In the same way the histories of patients suspected of having tuberculosis might well be canvassed for evidences of purpura, erythema multiforme and erythema nodosum. In my experience with the larger group of tuberculids I have been

impressed many times with the fact that a rheumatoid onset in this group of dermatoses should suggest tuberculosis almost as promptly as it does a focus of streptococcal infection. Arthritic and myalgic symptoms seem to have little differential value in eliminating tuberculous infection in these cases. Since the evidences of associated tuberculous infection in this group of conditions are largely objective, painstaking examination of the chest for physical signs, and by roentgenograms should be made in every case. The throat and accessory sinuses should be examined for a collateral focus of pyogenic infection and a radiogram of the teeth should also be a part of the routine examination. Systematic observation of the temperature should be undertaken, with a leukocyte count. A careful search for enlarged glands should be made and repeated. I believe that cases of erythema nodosum are of sufficiently grave prognostic significance to warrant a period of observation and reëxamination, prolonged in proportion to the suspicions developed by the study of the case. Finally, I venture to suggest the aid which dermatological consultation can render in such cases. One is surprised to see the readiness with which competent and even highly trained internists dismiss a purpura as "rheumatic," failing entirely to notice the tuberculid, or its scars, which lie beside it, or speculate on the probability of Hodgkin's disease in an adenitis when the evidence to prove it tuberculous is before their eyes in the form of a crop of papulonecrotic lesions. A certain amount of special experience and some special attention to this detail will add much to the diagnostic armamentarium of men in other fields who are called on to diagnose and deal with tuberculosis as a medical and surgical problem.

Conclusions. 1. While it is impossible at the present time to dogmatize on the existence of a tuberculous type of purpura, erythema multiforme or erythema nodosum, clinical and experimental evidence is collecting to show a close association between a tuberculous infection and cutaneous syndromes of the type mentioned. Whether the lesions themselves are due to the tubercle bacillus, and whether or not their appearance signalizes a flare-up in the tuberculous focus, cannot as yet be definitely stated. It is possible that a non-tuberculous infection which produces the erythema complex may uncover the tuberculous focus, so to speak, much as measles is known to do, and permit a lighting up of a lesion otherwise quiescent. The transition stages apparently existing between erythema nodosum on the one hand and erythema induratum and the tuberculids on the other, together with the experimental evidence cited, would seem to make this view the less probable one. The more probable one, in my opinion, is that which harmonizes with current conceptions of the etiology of tuberculids—that the purpuric, erythematous and nodose lesions are cutaneous reactions to hematogenously distributed tubercle bacilli, deposited in a hypersensitive

skin and originating in a tuberculous focus sometimes unrecognized perhaps for many years. Whether the tuberculous phase is the cause or the consequence, the frequent clinical association of the cutaneous symptoms with this disease loses none of its importance from the standpoint of diagnosis and therapy.

2. Since the clinical appearance of the eruptions discussed does not in my opinion offer adequate means of differentiating "tuberculous" from non-tuberculous forms, every case of purpura, and many cases of erythema multiforme, should, I believe, be subjected to a preliminary survey for the possibility of tuberculous infection. Every case of erythema nodosum should be subjected to an even more searching examination.

3. The search for a focus of tuberculosis should employ the usual evidence elicited from the history, weight and temperature curves and radiograms and physical examination for pulmonary and glandular signs (present in 8 out of 10 of the cases) here presented. The teeth and the nose and throat should be systematically examined for collateral foci of pyogenic infection, and dermatological consultation sought for seemingly trivial lesions on the fingers, face and legs, for scars and pustular lesions on the trunk, macular pigmentation, etc., to say nothing of the more obvious cutaneous signs of tuberculosis, such as erythema induratum, papulonecrotic tuberculids and folliclis (present in 3 of our cases).

4. Cases of erythema nodosum, whatever their type, should be subjected to periodic reëxamination and observation.

5. In the absence of a demonstrable source of pyogenic infection, and even in its presence, the possibility of tuberculous etiology should be seriously entertained and an antituberculosis hygiene considered.

6. The results of the application of the foregoing principles and routine to the dermatoses mentioned, while only partial as yet, have shown so high a percentage of demonstrable and suspected tuberculosis, pulmonary and glandular, osseous and cutaneous, as to lead the writer to suspect that the association is more than coincidental and that it can safely be made a basis for diagnostic and therapeutic decisions in a considerable percentage of cases.

7. It seems not improbable that erythema nodosum especially may be a syndrome of tuberculous as well as diphtheroid or streptococcal origin in an as yet unestablished percentage of cases.

8. Erythema induratum would seem to be susceptible of interpretation as, in a sense, a chronic ulcerative phase of tuberculous erythema nodosum, since intermediate types appear in this series.

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ACUTE PULMONARY EMPHYSEMA OBSERVED DURING THE EPIDEMIC OF INFLUENZAL PNEUMONIA AT CAMP HANCOCK, GEORGIA.

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Prior to the epidemic of influenza at Camp Hancock there occurred in one company an outbreak of hemolytic streptococcus infection of peculiar virulence and uniform course. There was reason for thinking that the spread of disease in these cases was by food or milk infection. One man primarily developed this trouble and in a few days six other men were affected simultaneously, all showing

aphonia, paresis of the soft palate, inability to swallow on account of choking, substernal pain, but otherwise no other subjective symptoms except cough. The expectoration became more profuse, bronchitis developed and three of the seven patients died. The temperature and pulse in all of these patients was practically normal throughout the course of their illness. Dyspnea developed as bronchitis increased, and it seemed to us that these patients really were drowned by the thick pus which they were unable to expel from the bronchi and trachea. Autopsy in these cases showed a streptococcus infection, with a remarkable affinity for the trachea, and gradually extending down through the bronchi. There was visible peribronchitis and peritracheitis. The larynx and the lungs escaped invasion. This series of cases is mentioned because there were many points of similarity with the bronchitis which accompanied influenzal infection later, and which showed uniformly a bronchitis and peribronchitis very similar to these cases but accompanied by pulmonary emphysema and so-called bronchopneumonia.

During the latter part of September there appeared at the camp an outbreak of disease which did not resemble influenza clinically, but which increased rapidly in frequency until during the last week of that month there were admitted to the hospital about 450 patients with this acute infection of the upper respiratory tract. These showed a mild coryza and conjunctivitis, some pharyngitis, very little bronchitis, frequently mild acute sinus symptoms and some slight cough, mild fever, brief course, and no severe pains. A number of cases of pneumonia developed among the patients. We had, during the epidemic, three wards of these so-called "Camp Hancock" pneumonias which were typical lobar pneumonia clinically. They all showed prune-juice or rusty sputum, high temperature, as a rule, with rapid course and termination by crisis. They all showed typical signs of consolidation in some portions of the lung. In many cases the course was brief after admission to the hospital, and, in fact, some of them seemed to be admitted just prior to crisis. We were able to keep those patients isolated from the bronchitis cases during the epidemic, and while the epidemic bronchitis wards were showing a mortality of nearly 40 per cent., there were only a few deaths among these pneumonia patients (under 5 per cent.) These acute upper respiratory infections, while not considered influenza at that time, appeared to exert a protecting influence when the real influenza appeared, and we were forced to the conclusion that an attenuated influenzal infection must have been responsible for the mild epidemic.

About October 1 there arrived at the camp over 2000 men who had become infected at another camp and had then been subjected to a prolonged railroad journey. The crossing of infections during this long journey produced a profound infection similar in all the patients and presented a very clear-cut clinical picture in this large group of

men. We admitted to the hospital in all about 1800 of these cases. They were characterized by:

1. Prostration—incident to the disease and added to by the fatigue, hunger and lack of care unavoidable during the long journey.

2. Cyanosis—particularly of the face and ears and intensely red conjunctivæ and dusky red pharynx.

3. Dyspnea—some degree of dyspnea was invariable; breathing was very shallow.

4. Epistaxis—very frequent, probably in nearly half the cases, and in many instances severe in degree.

5. Bloody sputum.

6. Cough—all had cough and showed signs of bronchitis in varying degrees of severity.

7. Extreme lethargy—a typhoid state, clear sensorium, but apathy and drowsiness; very few were delirious.

The patients suffering from influenza who recovered without marked pulmonary complications were, as a rule, convalescent within a few days and did not experience the nervous or renal complications which have been reported as so frequent in previous epidemics. Many of these men developed their bronchitic emphysema during the first day or two of influenza, others were apparently convalescent from the influenza and seemed ready for discharge to duty when there was a sudden onset of the so-called pneumonia, with characteristic change in the physical findings.

In the so-called pneumonic cases there was evident absent breathing, with impaired resonance at the bases and hyperresonance over the rest of the chest. We were struck with the burly appearance of these patients. This appearance was due to the distention of the neck vessels and erection of the chest, which was dilated to the full inspiratory limit. These patients showed increased temperature, with bloody sputa, and large areas of absent breath-sounds, diminished vocal fremitus, and above these areas crepitant rales in circumscribed zones and diffuse bronchitis throughout the lungs. Forced breathing might bring out rales where sounds had been absent. If breath-sounds reappeared the expiration was markedly prolonged. In no case was the sputum of the rusty or prune-juice type, but was foamy and bloody, and sometimes mixed so completely as to resemble tomato purée. Areas of dulness appeared in the bases, gradually spreading from below upward, and the sputum became frankly purulent or remained bloody, but was not viscid, as in pneumonia.

The temperature was irregular, always elevated but not unduly high; these patients might have sweating throughout the entire course of the disease. The pulse was slow for the temperature, suggesting reflex vagus inhibition from pulmonary distention. There was no arrhythmia and the heart remained apparently good

to the end. With the finding of dulness in the bases, which might occur within a few hours of the appearance of the areas of absent breathing, patches of tubular breathing would appear as in bronchopneumonia. These small areas of dulness rapidly coalesced until the whole base of the lung showed signs as in a lobar pneumonia, with marked percussion changes, sometimes flatness, and tubular breathing with egophony and whispered pectoriloquy, as in lobar pneumonia, often without rales.

The rapid massive involvement was accompanied or even preceded by the generalized pulmonary emphysema. Whether this was due to inflammation of the lung parenchyma, causing a loss of tone, or to nervous or circulatory trophic changes, causing loss of tonicity, or to bronchial blockage with valve action production is not clear and will not be discussed here. The sudden occurrence of profound emphysema in these cases as the outstanding feature of the condition was unmistakable. At this stage of consolidation, as at the prior stage of absent breathing, there was evident above the thus affected area a portion of the lung which was apparently compressed and showed diminished or absent breathing, impaired percussion note, and on forced breathing, or after hard coughing, showers of fine crepitant rales as the compressed lung unfolded. We consider this sign of changing areas of compressed lung a fairly constant sign of emphysema. The total lung volume is too great for the chest capacity, and some portion of the lung is usually compressed with other portions fully distended, these areas changing after deep breathing or coughing, with breath-sounds and percussion resonance being reëstablished in the expanding portions.

The areas of consolidation appeared usually posteriorly almost always on one side, followed by the other, spreading and coalescing toward the lower limits of the lung until the base was universally involved, then gradually spreading upward, one side more than the other, but seldom with one side wholly free from involvement. The total consolidation appeared as a gradual filling from below up. Bronchitis persisted throughout, but tubular breathing and pectoriloquy became pure in the solid portion, reaching perfection at the lower levels. Subcrepitant rales were typical in some portions.

The point that struck us here with great force was the intense dyspnea, with little cardiac disturbance, cyanosis, great air hunger, and erection of the chest fixed in a state of hyperinspiration, with only tidal air movement. As the muscles of respiration failed exitus occurred, a respiratory death, in contradistinction to the toxic circulatory or vasomotor death commonly seen in the early days of true pneumonia. The pulse impressed us as being slowed as if under the influence of cardiac vagotonic inhibition, as in high pulmonary pressure. The pulse in desperately ill or moribund individuals was excellent in volume and quality, and relatively slow; arrhythmias were almost never noted. As this distention of the chest developed

it could be noted that the whole chest excursion was diminishing as manifested by a general diminution of the lateral excursion of the costal arches until there was an inspiratory retraction, more in the affected side at the onset, then becoming bilateral.

Very soon the accessory muscles of respiration were the only effective ones giving a lift of the upper chest, while over the rest of the thorax was seen only a weak effort of the muscles, giving an undulatory movement of the chest, already so overdistended that any gain in capacity was impossible. Sternal tympany became more marked, assuming a box-like character. Marked stasis of all the veins entering the chest and those drained by the superior vena cava were manifest. Cyanosis became more profound and in the end stage there was an ashen lividity of the whole face and chest.

When in apparent respiratory extremis, frequently a patient would begin to complain of pains, substernal and in the jugular fossæ, and crepitation would be noted in the subcutaneous tissue at the root of the neck, and immediate marked subjective relief was apparent, rapidly followed by a noticeable improvement in the respiratory excursion of the chest, and the most striking decrease in cyanosis and jugular distention. With the relief of cerebral venous stasis a clearing up of the previous accumulative mental hebetude occurred with remarkable suddenness. Cutaneous emphysema soon became diffuse, not infrequently spreading down the trunk to the pubes, first appearing along the sheaths of the cutaneous veins. As the intrathoracic pressure was thus relieved these apparently moribund patients often went on to recovery. We then began measuring the respiratory excursion, the measurements being taken by Lieutenant Beveridge, and his measurements verified these clinical observations, in that there was apparent an increase in the chest circumference during the illness and an abnormally small respiratory excursion, with a striking increase immediately as the cutaneous emphysema gave vent to the air contained in the mediastinum.

The emphysema of the lungs and mediastinum was shown by the marked sternal and vertebral tympany, the disappearance of cardiac dulness and the low stand of the diaphragm, with the pleural sulci distended in full, marked limitation in the motion of the ribs, inspiratory retraction of the costal arches and marked cyanosis. The extent of the emphysema was so great that the supraclavicular and suprasternal fossæ were obliterated and the upper interspaces bulged on expiration and markedly on coughing. It was difficult to outline consolidations in the bases, because the percussion note over the whole chest was so hyperresonant and also because the lung tissue was found to be air-containing.

The course of the disease was entirely different from that of lobar pneumonia. This contrast was particularly striking, as we had at this time three wards of pneumonia patients, all of whom showed typical prune-juice sputa and termination of acute, severe, fre-

quently toxic courses by typical crisis. These cases, which were kept carefully isolated from newcomers, recovered without marked bronchitis and furnished an opportune contrast for comparative observation. We could not fail to be impressed by the presence in one group and the absence in the other of the characteristics noted above: namely, the peculiar type of sputum, cyanosis, dyspnea, respiratory movements and extreme emphysematous fixation of the chest, almost as in an animal in anaphylactic shock. Most of about 1800 patients received after a long railroad journey, with a profound degree of infection and thorough crossing of all the infectious strains, showed some degree of bronchitic emphysema and gave us an unusual opportunity for observing a condition developed to its greatest degree of uniformity and intensity.

The sequence in these cases is usually as follows: At the onset signs of generalized bronchitis and emphysema, universal throughout the lungs and most marked at the bases and toward the roots of the lungs. This is the stage of absent breath-sounds in the area which is about to show signs of consolidation.

Roentgen-ray plates taken at this stage are peculiar in that while the percussion note is resonant or hyperresonant throughout the chest, and the breath-sounds are diminished in intensity and not roughened, the skiagraph shows a diffuse clouding of the whole lung, with the bronchi clearly outlined, broad and dense, giving a streaked appearance, as in a moderate degree of bilateral fibroid phthisis.

The next stage showed continued universal bronchitis, with patches toward the bases showing the auscultatory signs of consolidation, which rapidly coalesced until these areas became diffuse, rapidly advancing upward, always bilateral, though the involvement in one side might be limited in extent. These signs were particularly well-marked in the back. The percussion note was altered by the emphysematous condition of the lung, so that a true flat note as elicited in pneumonic consolidations was not found. A note might sound almost flat in comparison with the hyperresonant or tympanitic note found in other portions of the chest, but careful analysis always has shown that there was a large factor of resonance or high-pitched tympany when this area was considered by itself. It may be noted here that these apparently solid lung portions all were air-containing and floated high in water. This is the stage in which the tympanitic note on the sternum becomes so marked, cyanosis and dyspnea extreme, the chest erected to its greatest capacity as if filled with a lung which is too large for the thoracic cage and the respiratory excursion practically obliterated. Toxic signs were not evident and pulse and temperature relatively low as compared with pneumonia. Delirium was comparatively infrequent and the anxiety and mental distress so marked in pneumonia were strikingly absent.

A number of the patients dying in this stage of early emphysema

came to autopsy. The cause of death was evidently the mechanical obstruction of the return flow of the venous blood from the general circulation to the interior of the chest by the thoracic fixation interfering with the mass movement of the blood. Dilatation of the right heart cannot be demonstrated clinically in these cases possibly because of the overlying emphysematous lung and tympanitic sternum, and probably because these hearts are not dilated as in pneumonia and certainly not sufficiently dilated to account for the enormous distention of the superior and inferior vena cava as a prime factor in this stasis. This stasis in the large veins appeared to be due to the obstruction occasioned by increased intrathoracic

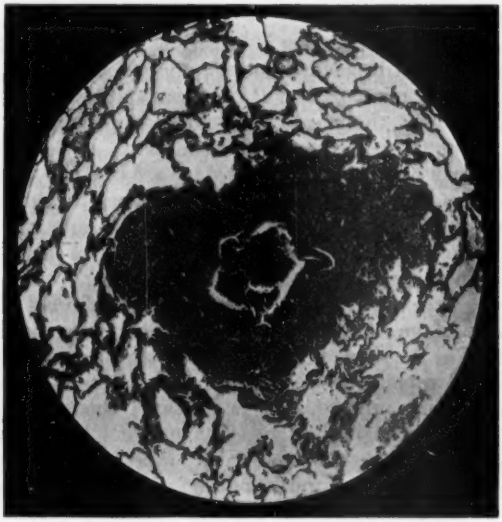


FIG. 1.—Bronchitis, peribronchial infiltration and acute emphysema, with turgescence and infiltration of the alveolar walls.

pressure, and the relief of stasis following immediately upon the escape of air from the mediastinum into the loose areolar tissue surrounding the large veins was one of the most striking features of the whole series of observations and was comparable to the relief afforded by venesection in the distress of acute cardiac dilatation.

While we had many autopsies showing this stage of the disease, one of the most graphic demonstrations of the extent of this emphysematous dilatation was afforded by the necropsy finding in the case of patient "G." In this case true lobar pneumonia supervened as a reinfection on an existing bronchitic emphysema and involved the upper and middle lobes on the right, making a perfect cast, measuring 40 cm., on the convex surface, 24 cm. on the concave and

15 cm. at the hilus. The rib markings deeply indented the surface. This cast by preventing any collapse of the lung showed the enormous distention which these lungs can attain.

The lungs of bronchitic emphysema at this stage showed a great similarity in gross pathology as well as in clinical findings. The lungs were gray toward the apex, with a uniform beefy red appearance toward the base. The surface was glistening, showed the rib markings and emphysematous bullæ, which were plainly visible under the visceral pleura. The emphysema was such that the lungs could not be collapsed by pressure, and while fairly tough at the apex were extremely friable at the bases. Here the tissue, while appar-

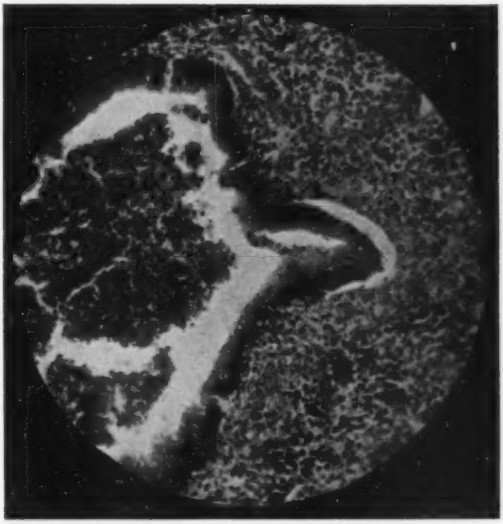


FIG. 2.—Portion of section shown in Fig. 1 under high power, showing changes in the columnar cells lining the bronchus, and the surrounding round-cell infiltration.

ently solid, was always found to be air-containing, floated in water, and although elastic to a light touch, disintegrated under moderate pressure, appearing almost necrotic.

The cut surface showed color as on the pleural surface, and from the red portions bloody serum exuded. The surface was glistening and pulled away from the bronchial stumps, which stood out prominently, showing thickened indurated walls and infiltrations surrounding them in cross and longitudinal sections and exuded thick, creamy pus. This poured out in quantity from the large bronchi. All lobes of the lung were studded with nodules from the size of a millet-seed to the size of a bean, which were inflammatory areas surrounding sections of the bronchi and bronchioles. Thick aggregations of

these formed irregular nodules, which simulated lobular consolidations; but to the touch these lungs had a feeling which was similar in all of them and quite characteristic. While the nodules varied in number and degree of coalescence they were distinct from lobular pneumonia, and of all pathological lung processes with which we are familiar they resembled only acute disseminated pulmonary tuberculosis. In looking at these lungs it seemed impossible that such lungs could clear up without multiple abscess formation or extensive necrosis. The lung parenchyma in the bases between these inflammatory nodules was mushy and friable. It seemed as though the blood supply and innervation must have been interfered with by the peribronchial infiltrations. The hard nodules were lacking in

FIG. 3.—Coalescence of peribronchial infiltrations in the evolution of consolidations.

those cases in which death occurred in the first days of the disease, but the same necrotic character of the lung parenchyma was present and the thickening of the bronchi evident. Pleural involvement was practically absent and empyema not found.

When convalescence was prompt and large abscesses or pleural fluids did not develop, the patients apparently recovered remarkably quickly and did not appear like men who had been through a course of pneumonia. The toxic depression was lacking and they looked remarkably well, but rales persisted throughout the chest and peribronchial fibrosis was marked. From the roentgen-ray plates one would say that there was present much lung destruction and permanent damage.

Other patients who were slow in convalescing showed an irregular temperature curve with febrile exacerbations, continued generalized bronchitis and purulent expectoration. The peribronchial thickenings and infiltrated areas, standing out clearly and separated by emphysematous lung, were so generally distributed and so close together in the roentgen-ray plates of these chests that the descriptive term "snow-storm" was applied to these plates. Multiple small abscesses were always present, thickly strewn throughout the lung, and these patients might die without the development of large areas of necrosis with empyema which frequently terminated the struggle for life.

FIG. 4.—Photograph of thoracic contents removed entire, showing large emphysematous bullæ of lung and particularly of mediastinal alveolar tissue. Specimen preserved in Kaiserling's fluid.

We encountered nothing resembling the primary empyema or extensive early pleural involvement accompanying the active pneumonia observed in the epidemics of bronchopneumonia of a year ago. When fluid was found in our cases it occurred late and seemed always due to a direct extension to the visceral pleura from an underlying inflammatory focus. The fluid always occurred late and if explored when first appearing was usually clear straw colored and coagulated promptly on withdrawal. If such a fluid was withdrawn by aspiration almost invariably sticky frictions were audible within a few hours. If reaccumulation of fluid occurred it was, as a

rule, distinctly purulent or sometimes fibrinous, making aspiration difficult.

Collections of fluid were in thin layers as if they had accumulated in the pleural cavities under pressure of the emphysematous lungs, which afforded insufficient space for the usual localization in the dependent portions of the chest and forced the fluid along the paths of least resistance, frequently upward and along the anterior mediastinum.

There was dulled tympany corresponding to the fluid, but percussion alone gave little distinction between areas of consolidation and fluid. These thin layers of fluid under high tension apparently served as excellent transmitters or conductors of voice and breath-sounds as well as of tympany to percussion from the compressed emphysematous lung beneath them. They did, however, act as mufflers in diminishing the amplitude of the vibratory waves, and we found that pure high-pitched tubular breathing, whispered pectoriloquy and egophony were the most reliable signs of fluid even though tympany was marked over these areas of effusion.

When the chest space was reduced by rapid collection of fluid in the pleural cavity, the emphysematous upper portions of the lung were pressed against the walls of the upper chest. These lungs (as noted invariably at autopsy) could not be collapsed by pressure, and the resulting signs were very different from those found where a normal or non-emphysematous lung is compressed by a large pleural effusion. We noted in these cases signs practically indistinguishable from those found in large cavities or open pneumothorax. The apices gave a perfect tympany to percussion and cracked-pot sound and a ringing character of the spoken voice, with amphoric transmission of tracheal breath-sounds. These localized fluid collections, rapidly walled off and under pressure, were frequently accompanied by severe diffuse pain in the axillary region of the affected side, with skin hyperesthesia and tenderness in the interspaces. It was noted that in the 6th, 7th, 8th, and 9th spaces, particularly the latter, the pain was constant even in the absence of respiratory motion, but accentuated on deep breathing or coughing.

The fluids varied in their bacteriological flora and in their physical characteristics. They were uniform in their late occurrence, sometimes six weeks from the onset of the bronchitis, from the fact that they were not the result of a diffuse pleuritis but started as exudates from relatively small areas of pleura overlying the inflamed or necrotic lung tissue. There was uniformity in the rapidity of formation of adhesions; indeed, so far as we could judge from physical signs and from autopsy findings the fluid was often found after adhesions had established themselves and started as softening in a mass of plastic exudate. Massive empyema was hardly ever encountered. A number of cases at autopsy showed the lung tissue at the bases so necrotic that we looked carefully in other patients for signs of lung

rupture and consequent empyema. This did not occur early, but eventually a number of patients showed rupture of lung abscesses into the pleural cavity. This rupture occurred after adhesions had formed and the empyemata thus developed were strictly localized and in some cases the bronchial drainage was sufficient to clear them up, at least temporarily. These patients with ruptured lung abscess frequently succumbed after a more or less prolonged septic course. The auscultatory signs of these conditions were well-marked and resembled those of large tuberculous cavitations, with whispered pectoriloquy and bubbling rales very close to the ear. The destruction of lung tissue by necrosis and abscess formation in these cases, as shown at autopsy, was enormous, almost total in the bases; usually parts of the upper lobes were also destroyed, the remaining lung tissue being markedly emphysematous.

Regarding treatment it must be said that no routine treatment was shown to be of value after the bronchitic emphysema was established. In view of the apparent immunity enjoyed by individuals who had recently suffered from attacks of probable influenza of a mild form it would seem that a proper vaccine might be of prophylactic value when influenza is epidemic. Creosote in full dosage in the influenza cases may be of service in preventing the development of bronchitis.

When bronchopneumonia with bronchitis and emphysema is established the therapeutic measures which are useful in the management of lobar pneumonia are of no avail. The emergency is due to mechanical rather than toxic causes, and the problems presented are totally different.

SUMMARY. Observation of 1150 soldiers with epidemic influenza pneumonia at Camp Hancock has indicated that the disease as it occurred there differed so essentially in its pathology and course from lobar, broncho- or lobular pneumonia, according to the usual conception of these diseases, that we designated the condition as Acute Bronchitic Emphysema.

Certain conditions were invariably present, including an intense bronchitis and peribronchitis similar to that found in a previous epidemic of pure hemolytic streptococcus infection. There was also present from the first a destructive softening of the lung parenchyma. In addition to this there was always an early and persisting generalized pulmonary emphysema which frequently was the main factor in causing death by interference with the mass movement of the venous blood. These conditions were found in every case examined at autopsy. Except for frequent acute otitis media there were almost no complications or sequelæ outside of the chest.

The pulmonary emphysema, with consequent venous stasis, accounted for the cyanosis, epistaxis and fixation of the chest in the phase of extreme inspiration, with low stand of the diaphragm, which characterized these cases, and also accounted for the paradoxical physical signs in cases in which fluid developed in the chest.

PRIMARY CARCINOMA OF THE THIRD PORTION OF THE DUODENUM.[1]

By George Douglas Head, M.D.,
MINNEAPOLIS, MINNESOTA.

Primary carcinoma of the duodenum is a rare disease. Only 7 cases are reported by Schleringer in 42,000 autopsies made in Vienna. Perry and Shaw in studying the Guy's Hospital Reports found only four examples in 18,000 autopsies. Out of 19,500 autopsies done at the London Hospital 18 cases were found.

Carcinoma of the duodenum comprises about 2 per cent. of the cases of primary malignant disease of the intestine. The disease may occur in any part of the duodenum. Of Fenwick's 57 collected cases the first part of the duodenum was involved in 21.5 per cent., the second part in 57 per cent., and the third in 13.5 per cent.

The majority of these tumors belong to the cylinder-celled type, but colloid cancer and spheroidal-celled types occur. Adenocarcinoma usually encircles the gut and causes a constriction of its lumen, while the spheroidal-celled carcinomata either take the form of soft excrescences or of deep ulcers, with elongated edges and fungated bases.

This case was an adenocarcinoma, involving the third portion of the duodenum below the biliary papilla. It encircled the bowel wall and produced almost complete occlusion. It was primary and no other organ was involved. Before proceeding to give the history of the case, I wish to review the symptomatology of the disease. The clinical picture presented depends upon the location of the growth in the duodenum. Carcinoma above the biliary papilla—namely, in the horizontal portion of the duodenum—presents the symptoms of pyloric stenosis, beginning with discomfort and flatulence after meals, with later pyrosis, loss of flesh, anemia and finally vomiting of a persistent type, with or without hematemesis. A palpable mass is usually present. Carcinoma in the vicinity of the biliary papilla—namely, in the second part—is ushered in with a slow developing icterus without pain or vomiting. Chills and fever may be present. The jaundice persists, vomiting develops, the liver becomes enlarged, the gall-bladder may be distended and palpable, there is progressive loss in weight and strength and the patient dies in inanition. A palpable mass may or may not be present.

In carcinoma of the third portion of the duodenum the first symptoms, according to Fenwick, consist of flatulence and discomfort after meals, burning acid eructations, loss of appetite and gradual emaciation. After a lapse of a few months vomiting appears and

[1] Presented before the Minnesota Pathological Society.

persists until the end. (In this case the vomiting was intermittent and there were months in which the patient was free from it.) The tongue becomes thickly coated and thirst becomes excessive. (In this case the tongue was clean.) There is marked cachexia and rapid loss in flesh. (In this case no real cachexia and no persistent loss in weight until near the close, but, on the contrary, a gain of eight to ten pounds during one interval of the illness.) The bowels are obstinately constipated. (In my case the bowels could always be moved by a saline.) The stools are seldom quite devoid of bile and often contain altered blood.

The character of the vomiting is an important feature. It always contains bile, which gives it a bright green color. The filtered vomited material is neutral or alkaline in reaction. (In this case it was acid.) It contains no free hydrochloric acid, but usually lactic acid. (The contents always contained free hydrochloric acid in the case reported and contained no lactic acid.) Will digest fibrin if warmed, owing to the fact that it contains pancreatic juice. (This test was not made in my case.) From time to time attacks of intestinal obstruction intervene, attended by incessant vomiting and obstinate constipation. At these times from 10 to 15 pints of an alkaline bilious fluid may be vomited in the twenty-four hours, notwithstanding the fact that the patient has taken nothing by mouth.

Examination of the abdomen shows a much enlarged stomach, with pronounced succussion as far out as the right mammary line. No tumor, as a rule, can be palpated unless the retroperitoneal glands are involved, when an ill-defined hard mass can be felt to the right of the umbilicus. The introduction of a stomach tube gives evidence of considerable importance. After the stomach has apparently been emptied a fresh gush of fluid gastric contents appears, with cough, or when the body is bent to the left, due to the regurgitation of the duodenal contents. After the stomach has been evacuated a succussion splash may be obtained to the right of the navel, owing to the presence of fluid in the duodenum. Finally, after emptying the stomach at night, a quantity of bilious fluid may be again extracted in the morning before food is taken.

Case History. Mr. G. H., aged seventy-four years, married, children, a man of large affairs. No cancer history in his parents. Had been strong and well as a young man. For the past seven or eight years had had distress in his upper abdomen and back from time to time. He was a very heavy eater, and these spells were attributed to indiscretions in his diet. The distress was never acute, but he would complain of some ill-defined soreness in the upper abdomen. He would often vomit once or twice. The spells never continued for more than a few days, and would then disappear. During the later years of his life he had been subject to attacks of bronchitis in the winter. In some of these his breathing had bothered

him, especially at night, and in one or two he had had some cardiac disturbance, with a weak, feeble, rapid pulse. Had had casts and a little albumin in his urine for years. Had taken a moderate amount of stimulants all his life.

In the latter part of November, 1916, following the death of his wife, it was noticed that he seemed pale in color and lacked his usual vigor and energy. No thorough examination was made at the time, as his attending physician attributed the state of health to the trying circumstances surrounding the death of his wife. He was sent to southern California for the winter. While going over the mountains the nurse noticed that he complained of distress in his chest and became pale and weak. After reaching Santiago he was thoroughly examined by an internist and a diagnosis of pernicious anemia was made. No nucleated reds were, however, found in his blood. The blood examination at that time showed 2,500,000 reds and 55 per cent. to 60 per cent. hemoglobin. He had some gastric symptoms in January, 1917, and one or two vomiting spells. In February he had more gastric distress, with vomiting lasting over a month's time. From this he recovered and felt splendidly for about a month, when he again had an attack of persistent vomiting lasting three or four days. He retained nothing upon his stomach during this attack, and the vomited material was dark brown in color. In this attack he vomited large quantities of fluid—in fact, more than he took in. He returned to Minneapolis in May, much improved, and the blood examination, made by his physician, showed 4,000,000 reds and hemoglobin 56 per cent.

I saw him first in June, 1917. He was in one of his vomiting attacks. Had been vomiting two days or so. Was getting up large quantities of dark and greenish-looking fluid, with many black, partially digested blood-clots in it. The fluid vomited was much more than he was ingesting. Would vomit a bowlful at a time. The appearance of the vomited material suggested cancer of the stomach, and this diagnosis had been considered on account of the man's age; but the absence of a palpable mass, the fact that he had maintained his weight, his perfect relief from gastric symptoms between attacks, his high-grade anemia and the negative roentgen-ray examination of the stomach for carcinoma had been considered sufficient evidence for ruling this out.

The physical examination revealed a large-framed, well-nourished man, with iron gray hair. The color of his skin and mucous membranes showed marked anemia, not the typical waxy color of pernicious anemia. He was weak from the vomiting, but had been up and about at home prior to this attack, and felt good. He complained of no numbness of the hands or feet. Nothing of importance was noted outside of his color, a systolic bruit at the apex of the heart, without cardiac enlargement, and a somewhat emphysematous chest with quiet breath-sounds. No enlarged glands or hard nodules in the

skin could be felt. A small lipoma, the size of a bean, was present in the abdominal wall of the upper right abdomen. This at first was confusing and was interpreted as intra-abdominal. No mass could be palpated in the abdomen. The rectal examination was negative. Distention of the stomach with gas showed a large stomach, the greater curvature being below the umbilicus. No mass could be palpated after gas distention. No peristaltic waves could be seen sweeping over the stomach. Marked succussion was present over the stomach area. The liver was not enlarged. The spleen not palpable. No masses could be palpated in other parts of the abdomen.

The examination of the vomited material showed a strongly acid reaction; free hydrochloric acid 6, total acidity 20; no lactic acid; strongly positive benzedine; no Oppler-Boas bacilli. The gastric analysis following an Ewald meal showed free hydrochloric acid 59; total acidity 100; no lactic acid; negative benzedine.

The blood examination showed hemoglobin 45 per cent.; reds, 3,900,000; leukocytes, 7000. Differential count: polynuclears, 71 per cent.; large mononuclears, 2 per cent.; small mononuclears, 23 per cent.; transitionals, 2 per cent.; basophiles, 2 per cent.; no myelocytes; no nucleated reds.

The urine was acid; specific gravity, 1018; contained some albumin; no sugar; an occasional pus cell; a few small, narrow hyaline and granular casts. The stools showed a strong benzedine test for blood.

We had then here to deal with an old man, well-nourished, looking very anemic, complaining of ill-defined gastric symptoms, exhibiting at times periodical attacks of vomiting of large quantities of greenish material, with partially digested blood, whose physical examination revealed a high-grade secondary anemia, without assignable cause except the presence of blood in the vomit and in the stools. Roentgenoscopic examination of the stomach and bowel was refused on account of a former unhappy experience when previous roentgen-ray examinations had been made.

The primary examination was made June 23, 1917. The patient was observed closely from that time until his death in coma, about seven months later, and one year and two months subsequent to the time when he first presented symptoms of anemia. I wish to give you as nearly as possible an outline of the clinical course, with the blood, gastric and stool studies during this period.

The note of June 27 read: I saw this patient at his house last night. Was feeling much better, retaining all his food. Says he does much better on a solid than on a liquid diet. Is now eating toast, soft eggs, breakfast foods, etc. I palpated the upper abdomen. Could feel the little-finger-sized nodule to the right of the median line, close to the right costal margin. It is tender to touch and not very hard. Could feel no enlarged

glands. No evidence of metastatic nodules or anything suggestive of malignant disease.

Note of July 7 read: Examined Mr. G. H. today. Patient is getting on very well on his diet of rice, milk toast and cereals. He has not vomited. He is not losing weight and feels good. In the mid-abdomen, about midway between the tip of the ensiform and the umbilicus, I could feel a deep-lying resistance, which I could not outline. This spot is tender to touch on firm pressure. Examination of the stools shows occult blood. Have placed the patient on treatment for duodenal ulcer.

July 16. Examined patient again today. Says he is comfortable, more so than he has been for a long time. Has had no vomiting. Could palpate no mass or tenderness in the abdomen. Is eating only rice and bread and milk. Is fed every two hours. Is gaining in weight. Occult blood is still present in the stools, but the reaction is not as pronounced as before. Blood examination shows hemoglobin, 64 per cent.; red cells, 3,732,000.

August 28. Patient feels much better. Is almost free from abdominal distress. No vomiting. Sleeps well. Still on soft diet. Is gaining in weight. Stools show occult blood. Can palpate no mass. Hemoglobin, 58 per cent.; reds, 3,253,000.

October 1. Patient looks a trifle paler. Up and about each day. Is complaining of a dull pain coming on from time to time in the lower right abdomen. It does not persist and lasts only for a minute or two. He has complained of this distress frequently. No mass could be palpated. The old area of tenderness in the upper mid-abdomen is not present. No enlarged lymph glands in the groins, axillæ or elsewhere can be palpated. Spleen not enlarged. Liver at the costal margin. Nurse states that for about a week stools have been a dark brown. Stool examinations show occult blood. Blood examination shows a sharp drop: hemoglobin, 36 per cent.; reds, 2,840,000; leukocytes, 5600. Differential count: polynuclears, 74.5 per cent.; large mononuclears, 2.5 per cent.; small mononuclears, 20.5 per cent.; transitionals, 2.5 per cent.; eosinophiles, 0; basophiles, 0; myelocytes, 0; no nucleated reds.

October 6. Examined patient today. Having all stools saved. The stools are lighter and have lost the dark brown color of a few days ago. Put an ice-bag again over the abdomen. The patient has evidently had more bleeding, which is now quieting down.

October 10. Stools are still lighter. Have still a greenish color. Dark brown color has disappeared. Patient complains of ill-defined distress in the upper abdomen. Calls it indigestion. Says it shifts from one point to another. Says it comes on after eating. Belches gas and it disappears.

October 16. Patient is not doing so well. Seems more prostrated and weak. Color is paler. Stools are much lighter, a pale green, but still contain blood by the benzedine test. Blood examination shows hemoglobin, 23 per cent.; reds, 3,184,000.

October 29. Patient is again better. His color is not so pale. The pain in the mid-back, which he has had for a number of days, has disappeared. Palpated the abdomen but could feel no mass. Stools still contain blood. Blood examination shows hemoglobin, 37 per cent.; reds, 3,232,000.

November 18. Examined Mr. G. H. today. Is doing fairly well. His color is better. Has gained some in weight. Complains very little of distress in the upper abdomen. Is eating a fairly general diet without distress. Stools are a typical milk stool, but show occult blood. Went over the abdomen carefully, but could palpate no mass.

December 16. Saw this patient today. Is doing splendidly. Color is improving. Is eating a fairly general diet, including fish and bacon and scraped beef, without distress. Blood examination is better: hemoglobin, 42 per cent.; reds, 4,016,000.

January 6, 1918. Patient is having distress in the upper abdomen, with belching of gas. Thinks it is due to sweetbreads which he had eaten. Has been eating all kinds of foods without distress up to this time. Stools are again a dark brown color and give a stronger benzedine test.

January 8. Patient was seized with a severe attack of vomiting in the night. Vomited, two or three times, a large amount, 500 to 1000 c.c. The material was a typical coffee-ground vomit. In spite of the fact that he took little fluids large quantities of dark material continued to come up. There was no tenderness in the abdomen. A marked succussion sound was present over the stomach area. The vomited material was acid, contained free hydrochloric acid, 12; total acidity, 34; no lactic acid; was strongly positive for blood by benzedine.

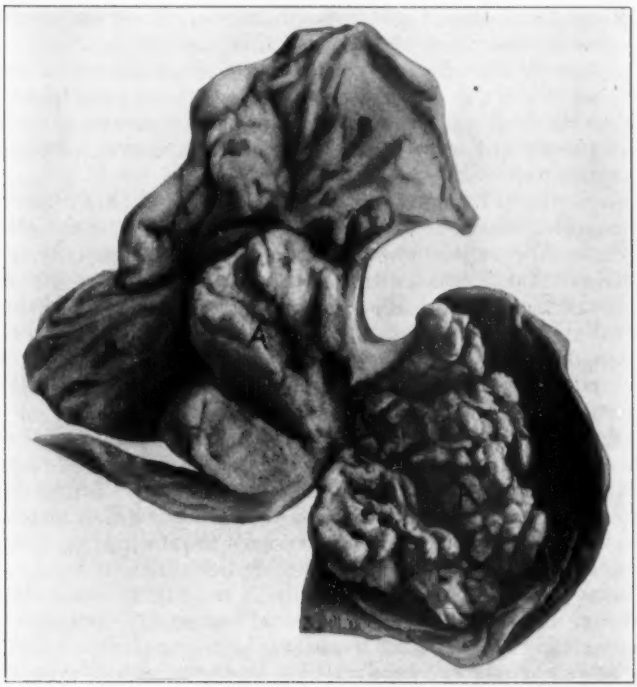
January 11. Patient today vomited a large amount of dark, grumous, black material, depositing a heavy sediment of small dark blood-clots on standing. Some of the last of the vomited material coming up contained bright blood. The vomited material was acid; contained free hydrochloric acid, 4; total acidity, 36; no lactic acid. Strongly positive benzedine test.

January 13. Patient is doing badly. Continues to vomit about 1000 c.c. of dark coffee-ground material four or five times a day. The vomiting attacks come in spells. Is taking plenty of fluids, and when the stomach becomes filled begins to vomit. Vomited material has no fecal odor. The vomiting, however, is of the obstructive type, as the stomach can be seen to slowly fill up with fluids and then empty itself, only to be filled again. Patient is rational, his pulse is good and the supply of fluid by rectum relieves his thirst.

January 17. Patient is losing ground. Vomiting still continues, all of a coffee-ground character, and in large amounts. He is becoming weak and prostrated. Anemia is marked. Patient is perfectly rational and is in no severe pain. The vomiting gives him relief.

January 19. Patient died today in coma. Vomited coffee-ground material only a few hours before his death.

With the completed clinical picture of the disease before us, one of two interpretations seems justified in a man aged seventy-four years, showing a high-grade anemia, with blood persistently in the stools, a hyperacid gastric content, no palpable mass, and dying with the symptoms of obstructive vomiting—namely, either a carcinoma high in the intestinal tract below the stomach or a duodenal ulcer with a carcinoma superimposed, causing obstruction by occlusion of the bowel. The diagnosis of the case prior to autopsy was a duodenal ulcer, with carcinoma superimposed, producing a slow-developing occlusion of the intestine not far from the pyloric opening.



Primary carcinoma of the duodenum. *A*, carcinoma; *B*, duodenal walls.

Postmortem Report. (By E. T. Bell, M.D., Professor of Pathology, University of Minnesota.) Autopsy limited to an abdominal incision. No evidence of disease in the peritoneal cavity. At the lower curve of the duodenum and extending over into the third portion a resistant mass was palpated. The stomach and upper part of the duodenum showed a moderate degree of distention.

Upon opening the duodenum a tumor mass was found situated mainly in the third portion and in the lower part of the descending portion. The lumen was almost completely occluded by a cauliflower-like growth growing from the median and posterior wall. This growth extends from a point 2 cm. below the papilla of Vater to a point 9 cm. below the same structure, the length of the tumor in the long axis of the duodenum being therefore 7 cm. The greatest height of the growth projecting into the lumen of the duodenum is 3 cm. At a point 4.5 cm. below the papilla of Vater the lumen of the duodenum is extremely narrowed, being almost completely obstructed. The point of attachment of the cauliflower-like growth to the inner posterior wall of the duodenum measures 4 cm. There is no involvement of the head of the pancreas, which lies in contact with the portion of the duodenum from which the tumor is growing. There is no enlargement of the lymph nodes in the abdominal cavity at any point.

Microscopic examination of the tumor shows a typical adenocarcinoma of the papillary type. Infiltration extends deep into the muscular layer of the duodenum on its inner aspect.

The kidney shows numerous coarse pits over the surfaces, particularly marked along the convex borders. There is, however, only a moderate reduction in the amount of renal cortex. Microscopic examination shows the lesion to be of the coarse arteriosclerotic type. There is no anatomical evidence suggestive of renal insufficiency.

No gross or microscopic lesions in the adrenals, liver, pancreas or lymph nodes around the celiac axis.

REPORT ON THE EXAMINATION AND TREATMENT OF SOLDIERS INFECTED WITH HOOKWORM AT CAMP BEAUREGARD, LA., MARCH 1 TO SEPTEMBER 1, 1918.

By Donald J. Frick, Major, M. C., U. S. A.,

This report is made for the purpose of showing the wide distribution of hookworm among Southern troops, the necessity of early examination and intensive and repeated treatment.

On account of a number of unavoidable circumstances, the examination for hookworm was not begun until the end of February, 1918. As the work was new to nearly all concerned, it was slow and not systematic. As a result, rather a large number escaped having their stools examined. After the examination was made and the list of positive cases fully determined, it was most difficult to get the men sent to the Base Hospital for treatment. The hospital had plans made to treat 100 cases every forty-eight hours, but was

hardly ever able to get more than 50, and sometimes only 15 or 20. As a result many men were sent overseas or to other camps before their turn came for treatment.

All examinations and treatment have been done practically since March, 1918, and the figures here given are for that time. The soldiers from which the statistics were gained were from the 39th Division and from troops sent in from time to time to fill out the division, several large contingents having been withdrawn for different purposes.

Table I shows the total number examined, with the positive cases and the percentages. The percentage of positive cases for all white troops was 11.5 per cent.; the percentage of positive cases in the colored troops was 1.1 per cent., a remarkable disparity and one that can be explained only by the fact that the negroes do not live in the hills where there is sandy soil, but come from the delta region.

TABLE I.

No. of cases.	From.	States.	Color.	Number positive.	Percentage positive.
18,390	39th Division	Louisiana, Arkansas and Mississippi	W.	2423	13.7
4,235	May draft	Louisiana, Arkansas and Mississippi	W.	365	9.0
2,217	Camp Pike	Missouri, Kentucky and Arkansas	W.	85	4.0
100	Camp Pike	.....	C.	2	2.0
1,407	July 29 draft	Louisiana	C.	16	1.1

The percentage of positive cases from these three States, Louisiana, Arkansas and Mississippi, was 12.3 per cent. Unfortunately we have no record of the actual number of cases that were positive from each State, so we cannot give figures for them separately; we can get an approximate idea from the cases treated.

Of the 2891 positive cases 1621 have been treated once and about 50 cases twice. These cases were sent in at random and probably fairly well represent all the organizations examined.

The three principal States gave the following figures: Louisiana, 898 cases; Mississippi, 454 cases; Arkansas, 243 cases; from all other States, 126 cases.

As the 39th Division, from which most of these figures were taken, was apparently about one-half from Arkansas and one-quarter from Louisiana and Mississippi, the high rate of infection in Louisiana is shown.

The first 1100 cases taken into the hospital were thoroughly examined and histories taken. From the tabulations of these statistics the figures for the rest of this paper are drawn. As there was no attempt at system in sending these cases into the hospital they well represent conditions in the troops at Beauregard.

There were 1100 cases studied and tabulated, as follows:

Louisiana, 64 parishes, 537 cases; Mississippi, 81 counties, 325 cases; Arkansas, 74 counties, 181 cases; other States, 57 cases.

The parish or county from which each infected soldier came was ascertained. The prevalence of hookworm in all three States is best shown by a review of these figures:

Louisiana, 64 parishes: 6 parishes gave 0 cases; 22 parishes gave from 1 to 4 cases; 36 parishes gave from 5 to 122 cases.

All four corners of the State and the middle were represented, the parishes along the Mississippi River yielding very few cases; 15 parishes, not counting Baton Rouge and Orleans, yielding 24 cases, less than 2 per parish. This condition prevails in the river counties of Arkansas and Mississippi:

Mississippi, 81 counties: 8 counties, 0 cases; 38 counties, 1 to 4 cases; 35 counties, 5 to 31 cases.

The cases were distributed throughout the State as in Louisiana:

Arkansas, 74 counties: 8 counties, 0 cases; 66 counties, 1 to 11 cases.

The small number of cases in all parts of Arkansas as compared with Louisiana and Mississippi is very striking.

The cases from all other States are listed below simply to show the necessity of hookworm study in all Southern camps.

STATES.

Alabama	12
Texas	23
Missouri	3
Oklahoma	1
Tennessee	4
Georgia	7
North Carolina	3
California	2
Virginia	1
South Carolina	3
	59

TABLE II.

The natural supposition that more farmers are infected than men with other occupations is shown by these statistics to be true, although all occupations, skilled and unskilled, seem to be touched by it.

Farmers	671
Lumber industry	78
Clerical	66
Miscellaneous	79
Mechanics	51
Students	48
Railroad men	42
Carpenters	22
Salesmen	17
Druggists	3
Musician	1
Butchers	2
Hostler	1
Lawyers	3
Bakers	5
Teachers	10
Factory workers	6
Total	1100

TABLE III.

The description of the kind of houses was not of much avail except to show the large number of box and log houses still occupied by these men, with the imaginable surroundings.

Frame houses	831
Box houses	227
Log houses	36
Brick houses	5
Tent	1
	1100

TABLE IV.

From the proved fact that water may be contaminated the source of water supply has interest. The 86 using city water, the 72 using artesian water and the 96 who had bored wells were the only ones that were immune from this source of infection.

Well (kind unknown)	422
Well (open)	163
Well (bored)	96
Cistern	88
City water	86
Spring water	73
Artesian water	72
Pump	62
Well (dug)	17
River water	16
No record	1
Pond	1
Condensed	1
Tank	1
	1100

TABLE V.

The fact that nearly 70 per cent. came from a country that has a sandy soil corroborates what has been known before.

CHARACTER OF SOIL.

Black	88
Clay	272
Sandy	740
	1100

TABLE VI.

The statement of 823 of these soldiers that there were no other cases in their family would hardly seem to point to the fact that it did not exist, but rather to the fact that diagnosis and treatment of hookworm have been very much neglected in these districts.

NUMBER IN FAMILY WITH HOOKWORM.

Cases in family.	Number.
0	823
1	80
2	45
3	26
4	20
5	9
6	1
7	2
8	3
9	3
10	1
11	1
12	1
No record	85
	1100

TABLE VII.

The high average of intelligence of these cases makes the answers of more value and shows the absolute neglect and disregard of the disease; 72 per cent. of these men had had seven years or more of schooling; 20 per cent. had four years in the high school or better.

GRADE REACHED IN SCHOOL.

Grade.	Number.
0	48
1	11
2	27
3	42
4	66
5	55
6	71
7	142
8	140
1 year, H. S.	120
2 years, H. S.	80
3 years, H. S.	95
4 years, H. S.	142
College	61
	1100

TABLE VIII.

Wearing shoes evidently follows education, as shown by the figure below. These men, however, are not far enough away from the period when all males go barefooted to make these figures important.

NUMBER OF CASES WEARING SHOES ALL THE TIME.

Yes	763
No	337

TABLE IX.

These men were of average cleanliness, apparently, so their infection could not be placed upon a basis of lack of care of their skin.

BATHS PER WEEK.

No. baths.	Men.
1	1 every two weeks
1	120
2	430
3	371
4	85
5	18
6	15
7	68
No record	4

TABLE X.

700 took baths in places safe from contamination; the other 400 certainly courted infection through bare feet when bathing.

BATHS, WHERE TAKEN.

Bath tub	650
Creek	276
River	85
Shower	49
Pool	14
Lake	12
Salt water	11
Pond	9
Spring	2

To get an idea of the degree of disability caused by this disease, the men were scrutinized closely and any symptoms that might be due to the disease were tabulated.

1028 of these men were healthy, fine specimens of manhood.

72 looked pale, weak and listless.

66 had had diarrhea at times through life.

1034 None.

233 had had indigestion at times.

877 had none.

347 had had headaches.

753 had none.

633 acknowledge having had ground itch.

467 had never had it.

Of these men 172, or 15 per cent., had had typhoid fever, giving some evidence of their sanitary surroundings.

219 of the cases of hookworm had been diagnosed before coming into the service.

TABLE XI.

Hemoglobin estimation is interesting, as it shows what little effect the infection has had on the majority of this group. Unfortunately the laboratory only had time to make the estimation on 612 cases.

HEMOGLOBIN.

No.	Cases.
60	2
70	44
80 to 85	364
86 to 90	158
91 to 95	28
96 to 100	16

TABLE XII.

The eosinophile count seems to verify the fact that an increase in the percentage is, in the majority of cases, found in hookworm. Counting 1 to 3 per cent. as normal, the height of the count apparently bears no relation to the severity of the case as judged by the condition of the patient. Those having an eosinophilia of 26 to 40, all were noted as healthy and only 1 had a hemoglobin of 70 per cent.; all the others were 80 per cent. or more.

EOSINOPHILES.

No.	Cases.
1	9
1 to 3	310
4 to 6	440
7 to 10	171
11 to 15	80
16 to 20	55
21 to 25	17
26 to 40	18

TREATMENT. A routine was followed from the beginning and carried through without variation. The soldiers were sent to the Base Hospital in groups of 20 to 135, usually after the noon meal. Early in the afternoon they were given a dose of salts; at 5 P.M. a thin broth; at 6.30 P.M. more salts. The next morning at 6 A.M. a third dose of salts. At 8 A.M. and 10 A.M., 1 c.c. of oil of chenopodium. This was followed an hour later by an ounce of castor oil in orange juice. In the middle of the afternoon they were given some liquid nourishment and at 5 P.M. a full meal. The next morning, after breakfast, they were returned to their companies.

Of the 1100, 307 had slight vertigo and 154 pricking in the hands and feet; 32 were either retained to be treated in hospital or sent home in the ambulance. The remainder marched back the three or four miles to their companies.

The oil of chenopodium was purchased in bulk and poured into capsules or given on sugar.

The result of the treatment and its efficacy cannot be established, as only 435 of the cases were reëxamined. Of these 84 were found positive, giving us an apparent sterilization of 80 per cent. in these cases.

The following method of collecting and examining hookworm specimens was used in the latter part of this work and found satisfactory.

1. A roster in duplicate is furnished the laboratory by the company commander through his medical officer, both of which are numbered serially and the original returned to the company commander, who directs the specimens to be collected in paraffin-paper sputum boxes. Each box has on it the serial number taken from the roster, corresponding to the name of the man who is to furnish the specimen in it. The specimens are then collected by companies, placed in boxes and delivered to the laboratory. A rubber band should be placed around each box to prevent it from coming open.

2. A test-tube (10 mm. x 10 cm.) is slipped under the rubber band of each box after having had placed on it the serial number of the box to which it is attached. Each specimen now has its individual test-tube.

KOFOID AND BARBER METHOD OF HOOKWORM EXAMINATION. (MODIFIED BY CAPTAINS BIRGE AND HENDERSON). 1. Fecal specimens collected in paraffin-paper sputum boxes numbered with roster of men, arranged in order.

2. Flotation of ova is accomplished by stirring a portion of feces (portion about the size of a small acorn) in a test-tube (10 mm. x 10 cm.), with concentrated brine, with a wooden stick, and let stand a few minutes until the debris sinks; the ova float.

3. With a wire loop, about 5 mm. in diameter, lift the surface of the concentrated solution and place on a slide for microscopic detection of the ova. No cover-glass is necessary. The ova are best seen with the condenser removed.

4. All intestinal parasite ova float near the surface of the portion placed on the slide and are easily found.

5. This method of examining for intestinal parasite ova has been very satisfactory.

CONCLUSIONS. 1. Hookworm is present in a large percentage of the soldiers from the South.

2. The colored soldiers of Louisiana show a remarkably low incidence of infection, less than 12 per 1000.

3. Hookworm apparently has no marked effect on the health of the great majority of these men. This may be due to the mildness of the infection or the fit condition of the men through training.

4. The early and repeated treatment of these cases is a necessity, so that they may not infect other localities, and because of the possibility that this infection may be a cause of lowering the soldier's resistance to other infections.

5. Treatment with oil of chenopodium is harmless and the routine suggested can be carried out anywhere that the men can be kept away from food.

6. On account of the better results shown in the Rockefeller Foundation Commission Report[1] by the use of milk in the morning and omission of purgatives, certain changes in our routine would be wise.

[1] Jour. Am. Med. Assn., February 22, 1918, pp. 499–507.

PLAN FOR EXAMINATION AND TREATMENT OF HOOKWORM CARRIERS IN SOUTHERN CAMPS. 1. A field laboratory will be established in the detention camp where all recruits are held in quarantine, this laboratory to be equipped to handle from 500 to 1000 stools per day. The men for this work may be detached temporaily from the Base Hospital.

2. The roster of each company in this detention camp will be sent to the laboratory. On the second day after the recruits are mobilized, stools of companies as designated by the commanding officer of this camp will be sent in, properly labelled, with the names of the men. The stools will be checked against the roster and opposite the names; after the examination is made the findings will be placed.

3. As soon as one hundred or more cases are found positive, these men will temporarily be confined to quarters for thirty-six hours and given the treatment.

4. All soldiers so confined should have at 4.30 P.M. clear broth; at 6 P.M. salts and another dose of salts at 5.30 A.M. the next day. At 6 A.M. a glass of milk. At 8 A.M. and 10 A.M. 1 c.c. of oil of chenopodium will be given. Castor oil, one ounce, or salts at 12 M. Soup at 2.30 P.M. and the regular meal in the evening.

5. From day to day all positive cases should be treated until all recruits with positive stools have gone through with the above routine.

6. One month after the first examination and treatment the laboratory shall send the roster of all names of soldiers who were found positive to the division surgeon, who shall order the stools of these men collected and sent to the laboratory of the Base Hospital for examination.

7. The names of all those having positive stools on the second examination will be sent to the division surgeon, who will have all these men mobilized to be sent to a field hospital or the Base Hospital for another course of treatment.

8. Upon the success of this plan, as shown by percentages cured, must rest the future treatment of these cases.

9. The advantages of this plan are: (*a*) Simplicity; no special material needed. (*b*) No loss of time, as the men will be in quarantine and only beginning training. (*c*) The assurance of getting all the stools. (*d*) The assurance of being able to treat all positive cases once. (*e*) The benefit to the men of getting rid of most of their parasites, which should help raise their resistance to other diseases. (*f*) A large decrease in the number of days in the hospital for every man with hookworm; therefore a better sick record for the camp.

NOTE.—Full credit is to be given Major James B. Guthrie, who inaugurated this work; to Lieutenant Joel B. Eastman and Lieutenant McNeese, for the collection of data and taking of histories. The laboratory work has been directed throughout by Captain E. G. Birge and Captain R. C. Henderson.

GRANULAR TUBERCULOUS CONJUNCTIVITIS TREATED BY INSTILLATIONS OF TUBERCULIN.[1]

By Robert C. Paterson, M.D.,
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The following case is reported to call attention to a method of treating a subacute tuberculous condition of the conjunctiva which, so far as I know, has not been previously employed except by Ellis and Gay,[2] whose article came to my notice after treatment had been inaugurated. This case also demonstrates the beneficial effects of controllable focal reactions produced by tuberculin on tuberculous tissues.

Case History. C. S., male, clerk in a shipping office, aged twenty-three years. Has had symptoms of pulmonary tuberculosis since the early summer of 1916. Examination of the chest shows a marked infiltration of the right upper and middle lobes and to a lesser extent in the lower part of the left upper lobe. Tubercle bacilli were present in the sputum. There is some involvement of the larynx, with marked hoarseness, for the past eighteen months. Although he has had hemoptysis on several occasions, the course of the disease has been one of slow improvement. In May, 1917, the patient first noticed that the left eye was inflamed, and pain, which was severe enough to keep him awake at nights, was felt in the eye and forehead. Reading increased the pain; there was little discharge and the lids were never glued together in the morning; there was no photophobia; vision was said to be somewhat blurred; there was no fever associated with this condition. I first saw the patient early in August, 1917, at which time the inner part of the left bulbar conjunctiva and the part below the cornea were covered with pale, sluggish, trachoma-like granulations, which were also present on the conjunctival surfaces of both eyelids, especially the lower. There was some injection of the conjunctival vessels; no ulceration was present and there were no definite tubercles. The cornea was not involved. There was no enlargement of the preauricular lymph nodes. A small amount of mucoid secretion was present, but this was not marked. Cultures from the conjunctival sac revealed staphylococci and a large Gram-positive bacillus. The condition failed to respond to the ordinary eye washes and astringents. With the approval of Dr. E. R. Baldwin, who agreed that the condition was probably tuberculous, on August 17, 2 drops of a 0.00001 dilution of O. T. were instilled directly into the left conjunctival sac. No reaction followed this, and on August 21, 2 drops of 0.0001 O. T. were instilled likewise without reaction. On August 24, 2 drops of

[1] Read before the American Climatological and Clinical Association, June 5, 1918.
[2] Lancet, August 4, 1917, No. 4901, cxciii, 156.

0.001 O. T. were instilled and 2 drops of this same solution were again introduced four days later, no reaction following in either case. On September 6, 2 drops of 1 per cent. solution of O. T. were instilled into the left conjunctival sac, and this was followed by a sharp local reaction, characterized by increase in the pain during the evening of the day on which the instillation was made by marked increase in the amount of secretion, which became thick and yellowish, causing the eyelids to stick together. There was marked dilatation of all the conjunctival vessels and swelling of the conjunctiva and lids. This reaction passed off within forty-eight hours, by the end of which time the conjunctiva appeared clearer and the granulations were smaller than before the treatment. Ten days later a similar dose, namely, 2 drops of 1 per cent. solution, was instilled and almost immediately a dilatation of the conjunctival vessels could be seen and a sharp reaction followed, as in the former instance. This treatment was continued for six doses, at about ten-day intervals, making in all eight treatments, with reactions, after which the conjunctiva showed little evidence of disease. All symptoms had entirely disappeared, and at the time of writing the only evidence of previous disease is a few fine granulations and slight reddening of the bulbar conjunctiva at the extreme inner canthus. The palpebral conjunctiva is clear, but there seems to be some thickening, as the palpebral slit is slightly narrower than that of the opposite eye and the patient is not able to open the affected eye quite as widely as the right. The lung condition and throat disease have been quiescent during the treatment and have not been affected by the reactions. The patient is now doing light office work for the first time in two years.

Discussion. Tuberculosis of the conjunctiva is one of the rarer localizations of this infection and may occur in the form of (1) ulcers, including lupus; (2) miliary tubercles; (3) granulations, including phlyctenules; (4) pedunculated tumors. A full description of these various forms and a general discussion of the subject of tuberculosis of the conjunctiva has been given by Eyres[3] in the Hunterian Lecture of 1912. Although tubercle bacilli were not demonstrated and no histological study was made of the granulations, as I did not care to excise any of the tissue for fear an ulcer would result at the site of the wound if bacilli were present in the granulations, the case here reported is in all probability one of tuberculosis of the conjunctiva. The clinical features in this case closely resembled the picture seen in Parinaud's conjunctivitis, except for the absence of enlargement of the preauricular lymph nodes, which is usually present in this disease. Möllers[4] has reported 2 cases of Parinaud's conjunctivitis, in which he demonstrated the presence of tubercle bacilli in the granulations by animal inoculation, and in this report quotes the

[3] Lancet, May 18, 1912, No. 4629, clxxxii, 1319.
[4] Veröffenthichungen der R. Kochsche Stiftung, Heft 4, 1913.

previous work of Wessely and others, who had proved the tuberculous nature of this disease. In this case the ordinary local tuberculin tests would not have assisted in diagnosis, as a positive reaction would have been obtained from the infection in the lungs, and although a subcutaneous test might have produced a focal conjunctival reaction, its use was contraindicated, owing to the danger of a general reaction on the pulmonary condition. The characteristics of the conjunctival lesion, the resistance to ordinary treatment, the presence of extensive tuberculosis elsewhere in the body and the marked focal reaction to tuberculin, followed by recovery, appear to justify the conclusion that the condition was a tuberculous one.

There has been much discussion and confusion as to the nature of the tuberculin reaction and as to how tuberculin aids in the cure of tuberculosis. Certain facts about the action of tuberculin are known, and a great many have been assumed without proof or sufficient experimental confirmation. Among these latter may be mentioned the production of antibodies of one kind or another in the serum and the development of a condition akin to anaphylaxis. The first of the known facts is that tuberculin has not a primary toxic action, even when used in enormous doses, on normal animals or persons, that is, on animals free from tuberculosis. Hamburger[5] reports having given 500 mg. of O. T. subcutaneously, without producing any general effects, to a child, which had failed to react to a previous skin test and which could, therefore, be considered non-tuberculous. Krause, working in the Saranac Laboratory, administered 25 c.c. of watery extract of tubercle bacilli intravenously to a normal guinea-pig without ill-effects, except for a watery diarrhea lasting a few days and caused by the rapid increase in the amount of fluid in the body. It may therefore be repeated that tuberculin has no deleterious effect on normal animals. Secondly, the presence of anatomic tubercle alters the body in some way so that all the tissues acquire a hypersensitiveness to tuberculin. This allergic condition or hypersensitiveness disappears when the tuberculous focus is completely healed or removed from the body. Thirdly, tuberculin acts specifically on tuberculous foci themselves, causing an acute inflammation in and around them. These focal reactions may be seen in experimental animals, killed during a general tuberculin reaction, and also are observed clinically in cases of tuberculosis where the disease is capable of direct observation, as in laryngeal and skin tuberculosis. The hyperemia accompanying this focal reaction permits of a dissemination of substances whose nature is not yet definitely known, and the entrance of these substances into the systemic circulation produces what is known as the general tuberculin reaction. The focal reaction thus produced by tuberculin may be a source of danger if the reaction is so great as to

[5] München. med. Wchnschr., 9 Juni, 1908, No. 23, I, 1220.

lead to a dissemination of bacilli to previously healthy tissues. On the other hand, if these reactions are slight and controllable the result of the inflammation is a tendency to walling off of the diseased focus by fibrosis, which is what we know as healing. The immediate object of tuberculin treatment should therefore be the production of slight and controllable reaction around the focus of disease. While this is simple when thus stated, it is not so simple in practice, particularly in pulmonary cases, for we are here dealing with a multiplicity of small foci in varying stages of development, from early and recent cellular tubercles to older, more or less fibrous or caseonecrotic tubercles, which will be influenced differently by the same dose of tuberculin. If we add to this difficulty the fact that our methods of observing and estimating the results clinically are relatively coarse and depend chiefly on the patient's subjective symptoms, the difficulties and chances of error in judging the effects of our dosage are apparent.

The case here reported shows the beneficial results of such focal reactions, and a clearing up of the granulations was noticeable after each reaction. In this case it would have been unwise to give tuberculin subcutaneously on account of the extent of the disease in the lungs, but fortunately the location of the disease in the conjunctiva permitted of direct application and direct observation of the results. As the reaction was purely local, the beneficial results cannot be attributed to changes in the serum nor to an alteration in the so-called general resistance of the system, but must be ascribed to local tissue changes. Whether a non-specific irritant, which would have produced an inflammatory reaction, would have brought about similar beneficial results cannot be stated or denied, as it was not tried, but the use of jequirity in granular eye conditions is an old method and might give grounds for the belief that this or other non-specific inflammation-producing remedy might have been equally efficacious.

STUDY OF AN UNUSUAL GLYCOSURIA.

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(From the Medical Laboratories of the Department of Medicine of the University of California.)

There has previously been reported a type of glycosuria in which while glucose was constantly excreted there were no symptoms of diabetes, the amount of sugar in the urine bore little or no relation to the amount of carbohydrate ingested and the blood sugar was normal. Klemperer,[1] who first noted this condition, found it associated with

[1] Verhandl. der Ver. f. inn. Med., Berlin, 1896, xvi, 67.

the evidences of a mild nephritis, and so named it renal diabetes. Since then others[2] have published cases in which the nephritis was not present, so that the condition has also received the name of Diabetes Innocens or Renal Glycosuria. Following the introduction of new chemical methods requiring only a few centimeters of blood for each determination,[3] the subject of blood sugar has been intensively studied. Investigators have found by taking samples of blood at frequent intervals that in the normal individual the blood sugar reaches its lowest point after a night's fast and rises soon after taking carbohydrate food into the stomach. From a half to one hour after the introduction of 100 grams of glucose into the fasting stomach the blood sugar rises from the normal level of 0.08 per cent. to 0.11 per cent. to not over 0.15 per cent., and falls within one and a half to two hours to below 0.11 per cent.[4] In diabetes the beginning of the blood sugar curve is frequently much above 0.11 per cent.[5] while in milder and less understood types of carbohydrate disturbance it may lie within or below the normal limits.[6] When the blood sugar rises to a point between 0.17 per cent. and 0.18 per cent., even in the normal individual, glucose is excreted in the urine and this point is spoken of as the kidney threshold for glucose.[4] Renal glycosuria implies a lowering of this threshold while the blood sugar response to a carbohydrate meal is normal.

While the following case seemed in many respects to fulfil the requirements of a renal glycosuria, this diagnosis could not be made because the blood sugar curve was abnormal. At the same time the failure to follow Allen's paradoxical law[7] made it improbable that the case was one of true diabetes. On account of its peculiar relation to renal glycosuria and a true error of carbohydrate metabolism I have thought this case worthy of report.

Case History. S. B., aged fifty-five years, a Polish Jew, entered the medical service of the University of California Hospital on May 17, 1918, and was discharged on June 8, 1918. He had syphilis at thirty-one and gonorrhea at thirty-four, with gleet for ten years afterward. Five weeks before admission he was seized with sharp substernal pain radiating down both arms and "into the teeth." There were no further attacks for one week, when they recommenced and grew steadily more frequent until he was having four or five in twenty-four hours. Sudden exertion brought on an attack

[2] Weiland, W.: Ueber einige Aetiologisch bemerkenswerte Diabetesformen, Deutsch. Arch. f. klin. Med., 1911, cii, 167.

[3] Lewis, R. C., and Benedict, S. R.: A Method for the Estimation of Sugar in Small Quantities of Blood, Jour. Biol. Chem., 1915, xx, 61.

[4] Hamman, L., and Hirschman, I. I.: Studies on Blood Sugar, Arch. Int. Med., 1907, xx, 761.

[5] Mosenthal, H. O., Clausen, S. W., and Hiller, A.: The Effect of Diet on Blood Sugar in Diabetes Mellitus, Arch. Int. Med., 1915, xxi, 93.

[6] Janney, N. W., and Isaacson, V. I.: A Blood Sugar Tolerance Test, Jour. Am. Med. Assn., 1918, 70, xvi, 1131.

[7] Allen, F. M.: Glycosuria and Diabetes, Harvard University Press, 1913, 72.

which nothing seemed to relieve. The pain present on admission lasted all day and was worse between 10 A.M. and noon, when he vomited.

Examination showed no signs of syphilis and the Wassermann reaction was negative. Along the fifth rib from the heart's apex to the sternum there was during the cardiac cycle a distinct scratching sound which was interpreted as pericardial friction. He had a leukocytosis of 25,000, which diminished to 12,000 during his stay in the hospital. The blood urea nitrogen was 8 mgm. per 100 c.c., and the phenolsulphonephthalein excretion 70 per cent. in two hours. A reducing sugar was found in his urine, and this gave typical crystals of glucosazone with Cipollina's test. Aside from the question of his glycosuria the clinical diagnosis was syphilis, arteriosclerosis with coronary thrombosis and subsequent pericarditis.

On May 20, when sugar was found in the urine, the patient was put on a prescribed weighed diet. After a preliminary observation period of three days, when he excreted from 5 to 11 grams of glucose per twenty-four hours, food was withdrawn, with the expectation that in twenty-four hours the urine would be sugar-free. Much to our surprise there was still a trace of sugar after two days' starvation. Food was then given again, the amounts of protein and fat being kept at the same level while the carbohydrate was regularly increased until it approximated the amount found in a normal diet. Practically the same amount of sugar was excreted on this diet as on the first day after starvation. Antisyphilitic medication was continued during the patient's stay in the hospital, and he had no further pain.

The urinary findings and the diet given are shown in Table I.

TABLE I.

Date.	Volume.	Total N.	Urea N.	Amm. N.	Creatinine.	Glucose.		Acetone body.	Protein.	Fat.	Cho.	Liquid intake.	Naked weight.
						Gm.	%						
May 21	840	12.00	.....	0.894	1.046	11.05	1.50	..	70	70	75	1500	55.0
22	800	12.91	.....	.666	1.029	5.41	.67	0	70	70	75	1500	55.2
23	1000	18.18	12.65	.450	.962	8.62	.80	0	70	70	75	1500	55.4
24	1300	10.24	8.17	.564	.916	Trace	....	..	0	0	0	3000	55.8
25	1360	17.00	11.13	.680	1.060	Trace	....	0	0	0	0	3000	54.8
26	1421	15.28	12.74	.789	.943	7.40	.51	0	54	52	67	1320	54.6
27	1420	15.96	12.33	.947	.928	6.46	.45	0	69	70	75	1500	53.4
28	860	10.36	8.43	.811	1.025	14.33	1.60	0	66	53	67	1350	53.4
29	1300	13.00	8.97	.492	.856	7.22	.55	0	70	70	75	1500	53.4
30	630	7.00	4.69	.242	.561	3.94	.62	0	away	part	of day		
31	1040	8.82	7.25	.495	1.154	4.41	.43	0	59	68	123	1500	53.0
June 1	970	8.01	.....	.....	.....	5.05	.52	..	70	68	150	1500	54.4
2	1190	13.68	.....	.....	.....	5.36	.45	..	70	70	250	1500	54.2
3	1620	11.55	.....	.....	.....	7.23	.44	..	70	70	250	1500	54.6
4	1450	8.95	.....	.....	.....	3.25	.22	..	70	70	250	1500	54.6
5	1500	7.24	.....	.....	.....	4.44	.29	..	70	70	299	1500	55.0

The blood sugar curve following 100 grams of glucose given June 6 after a night's fast, with the diuresis and amount of sugar excreted, are shown in the accompanying chart.

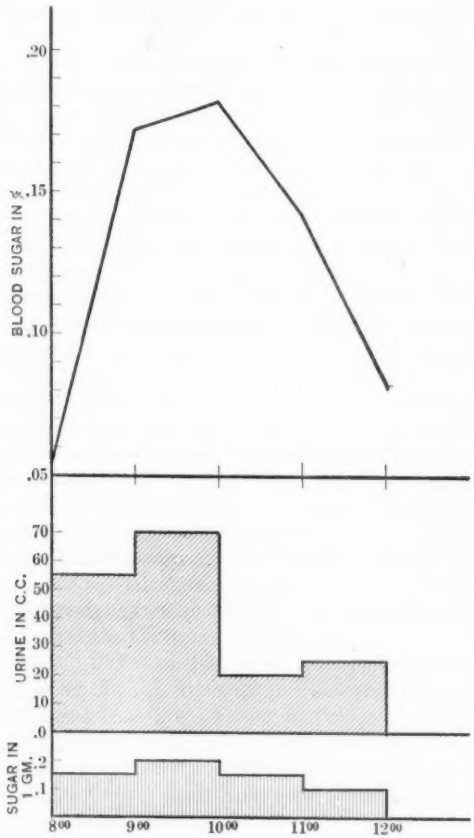

Table II shows the figures corresponding to the chart.

TABLE II.

Time.	Blood in sugar.	Urine in c.c.	Sugar in gms.
8 A.M.	.0566	464	
9	.1705	54	.166
10	.1807	70	.215
11	.1415	20	.166
12	.0789	24	.100

Folin's direct Nesslerization method[8] was used for the urinary nitrogen, his Permutit method[9] for the ammonia, the method of Van Slyke and Cullen[10] for the urea in the urine and blood, Folin's method[11] for the determination of the creatinine, Benedict's method[12] for the quantitation of the urinary sugar and the method of Lewis and Benedict[3] for the blood sugar.

SUMMARY. There were no symptoms of diabetes. The daily amount of sugar excreted by this patient varied from a trace to 14 grams but bore no relation to the amount of carbohydrate ingested except during the fast days, when only traces were found in the urine. A night's fast on June 5 sufficed to make the urine sugar-free at 8 A.M. the following day. The blood sugar was below normal at this time, but after 100 grams of glucose increased to above the normal expected rise and did not return to normal until the fourth hour. The percentage of glucose in the urine varied from 0.22 per cent. to 1.5 per cent., and was inversely proportional to the amount of urine. Kidney function was normal so far as could be determined by the phenolsulphonephthalein excretion and the blood-urea nitrogen.

DISCUSSION. Independence of the glucose excreted from the carbohydrate in the diet is not consistent with true diabetes, as Allen has shown, and it was felt from this patient's response to increased carbohydrate intake on fixed amounts of protein and fat that his glycosuria would prove to be entirely dependent on a low kidney threshold. Although the kidney threshold was determined between points too far apart to be of value (0.05 per cent., and 0.17 per cent.), it may be supposed that it was quite low, because during the two fast days when the blood sugar would perhaps not be expected to rise very much above the fasting level of 8 A.M. on June 6 (0.05 per cent.), traces of sugar were still excreted. This lowered threshold would satisfactorily explain the presence of the small amounts of glucose constantly found in this patient's urine. But when 100 grams of glucose were given after a night's fast, the blood sugar curve was found to show a higher rise than the normal expected one and a delayed fall. This type of curve has been found associated with mild diabetes and with ductless gland disease, and apparently demonstrated some abnormality of carbohydrate metabolism. We may suppose that this individual would have excreted a small amount of glucose only when the curve reached its highest point if

[8] Folin, O., and Denis, W.: Nitrogen Determination by Direct Nesslerization, Jour. Biol. Chem., 1916, xxvi, 473.

[9] Folin, O., and Bell, R. D.: Applications of a New Reagent for the Separation of Ammonia, Jour. Biol. Chem., 1917, xxix, 329.

[10] Van Slyke, D. D., and Cullen, G. E.: A Permanent Preparation of Urease and its Use in the Determination of Urea, Jour. Biol. Chem., 1914, xix, 211.

[11] Hawk, P. B.: Practical Physiological Chemistry, P. Blakiston's Son & Co., 1916, 506.

[12] Benedict, Stanley R.: The Detection and Estimation of Glucose in Urine, Jour. Am. Med. Assn., 1911, lvii, 1193.

the kidney threshold had not been low, so that the blood sugar response was not concerned with the glycosuria.

CONCLUSION. A case of gyclosuria with apparently lowered renal threshold for glucose is reported.

There was evidence of abnormal carbohydrate metabolism.

True diabetes was probably not present.

THE GRAHAM–STEELL MURMUR IN MITRAL STENOSIS.

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IN a number of cases of mitral stenosis there is heard at the left of the sternum in the region of the pulmonic valves, about the third intercostal space, a soft blowing diastolic murmur (Graham-Steell murmur). This has been ascribed to insufficiency of the pulmonic valves, due to dilatation of the pulmonic ring. Cabot[1] found this murmur in 22 out of 50 cases coming to autopsy, but on postmortem examination no recognizable lesion of the aortic or pulmonic valves was observed and no dilatation of the pulmonary artery. Thayer, on the other hand, in the discussion following the reading of Cabot's paper, states that when there was an opportunity of examining the heart after death he found in all cases with the Graham-Steell murmur marked dilatation of the right ventricle, with dilatation of the pulmonic ring.

The question which has interested us in a study of a rather large number of cases of mitral stenosis is in what proportion of cases this so-called Graham-Steell murmur is heard and what are its characteristics, so that there may be little difficulty in recognizing it. The Cardiovascular Board at Camp Jackson, consisting of four regularly appointed well-trained men and four men of exceptionable ability loaned for this work by Major Arthur E. Davis, of the 156th Depot Brigade, were instructed to refer to me all cases of mitral stenosis as well as all individuals of the draft who showed a snappy first sound at the apex, and all those who had a diastolic murmur, no matter where it was located, for detailed study. It was due to their painstaking care and hearty coöperation that a series of 36 cases of mitral stenosis were studied. These cases were definitely mitral stenosis and not aortic insufficiency, with a Flint murmur, although the differentiation may be at times difficult. This question will be made the subject of a subsequent communication.

Of the 36 cases, 24 were pure mitral stenosis, *i. e.*, with no insufficiency, and 12 were associated with a definite systolic murmur of an insufficiency. In the 36 cases a diastolic murmur along the left border of the sternum was heard 12 times, or in 33.3 per cent. of the

[1] Tr. Assn. Am. Phys., 1914, xxix, p. 22.

cases. In the 24 cases of pure stenosis it was heard 9 times, or 37.5 per cent., and in the 12 cases of stenosis with insufficiency it was heard 3 times, or 33.3 per cent. It would seem, therefore, that it is heard rather more frequently in the pure cases than in those associated with insufficiency.

The Graham-Steell murmur is a diastolic murmur heard at the left border of the sternum in some cases of mitral stenosis. It is especially well heard in the third left intercostal space. It may be described as a soft blowing diastolic murmur, which replaces the second sound at the pulmonic area. It may be heard when standing, but frequently it is missed entirely in the erect posture, and is brought out particularly well when the patient lies on his back. Occasionally, on the other hand, it is heard only when the patient stands. It is affected by respiration, and there is no definiteness in this. In some cases it is heard at the end of complete inspiration, in other cases at the end of expiration and again in the mid-period of quiet breathing. Exercise may intensify the murmur, and the patient should be examined following some effort. In some cases exerting pressure with the stethoscope will enable one to recognize the murmur. The duration of the murmur is variable—it may occupy the whole of diastole or only a part thereof. There is very little if any transmission.

Thayer has found hypertrophy of the right ventricle in his autopsied cases, but in our series, where there were no signs of decompensation, the right border, relying only on percussion, in no case extended farther than 3 cm. from the midsternal line. The reason for this discrepancy in findings is obvious. The response to exercise in mitral stenosis, as pointed out in another paper, is about equal between good and poor, and in cases with the Graham-Steell murmur we found 7 with good response and 5 with poor response to the effort of hopping on one foot 100 times.

The frequency with which a history of hemoptysis is given in mitral stenosis suggested the possibility that hemoptysis might be associated with the Graham-Steell murmur and might be the result of anatomical conditions producing the murmur. It was complained of 4 times, in 6 cases no history was obtained and in 2 cases the history was so uncertain that we prefer to classify these as indefinite. Comparing this with the cases with no Graham-Steell (24), we find that hemoptysis occurred 4 times, in 14 cases there was no history of hemoptysis and in 6 an indefinite history. Expressing the above in percentage:

In 36 cases of stenosis hemoptysis occurred 8 times, or 22.2 per cent.

Graham-Steell (12 cases).				No Graham-Steell (24 cases).			
Hemoptysis	4 times	or 33.3	per cent.	Hemoptysis	4 times	or 16.6	per cent.
Absent	6 "	or 50.0	"	Absent	14 "	or 58.3	"
Indefinite	2 "	or 16.6	"	Indefinite	6 "	or 25.0	"
		99.9	"			99.9	"

These numbers are rather small to permit of definite conclusions, but it is apparent that in our cases of mitral stenosis hemoptysis, when it occurred, was found more frequently when a Graham-Steell murmur was present.

The interest attached to the Graham-Steell murmur lies in the fact that it makes the differential diagnosis between aortic insufficiency with a Flint murmur and a mitral stenosis with a Graham-Steell murmur a matter of some difficulty. In searching for the murmur it is recommended that the patient be examined in various positions, in various phases of respiration and before and after exercise.

ON THE USE OF A BINOCULAR LOUPE FOR THE EXAMINATION OF THE FUNCTIONAL TROUBLES OF THE PUPIL.

By Dr. Emil Berger,

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It is a well-known fact that the iris is influenced by the different organs of the body, and particularly by the nervous system. The Swiss physiologist, Maurice Schiff (Geneva), therefore, rightly considers the iris as the esthesiometer of the human body. The examination of the functional troubles of the pupil are consequently of greatest importance not only for the ophthalmologist and neurologist, but also for medical science in general. Therefore the greatest interest has been shown toward experimental methods regarding functional troubles of the pupil. Such is the case particularly in respect to the reaction of the pupil to impressions of light.

Thirty years ago medical men examined this function by means of lighted matches, held before the eye of the patient; others used candlelight for this purpose or observed whether the darkening of the eye, caused by the hand being held before the eye and then withdrawn, influenced the size of the pupil. In present times the light-reaction of the pupil is tested by means of an electric pocket lamp. There is, however, still needful a more perfect method for observation of the functional trouble of the pupil. In the well-known manual on the relationship between ophthalmology and general medical science, Schmidt-Rimpler has already pointed out the utility of the binocular microscope for that purpose. In those times, however, the binocular microscope was a very expensive and unhandy instrument, for which reason it was not adaptable nor generally used by medical science. During the year 1899, Prof. J. Lippmann,[1] of the Academy of Science in Paris, demonstrated a very much simpler binocular loupe, and this has been recorded in the *Précis*

[1] Compt. rend. de l'Acad. des Sciences de Paris, November 23, 1899.

de physique biologique, by Prof. J. Weiss[2] and in the French *Encyclopaedia of Ophthalmology*.[3] I have in no way influenced the introduction and use of my binocular loupe in medical science, which employs it particularly in ophthalmology, dermatology and anatomy; it is chiefly Prof. Haltenhoff (Geneva), who has published a paper[4] on this subject. Having perceived, however, that one of the most important uses of my binocular loupe, that is, the examination of the functional troubles of the pupil, has been overlooked by physicians, I consider it my duty to correct this omittance by this short communication. I hope that soon the general use of the binocular loupe will take place. The observer will, however, bear in mind that such an examination has always to be performed at the maximum of the focus. I believe that the binocular loupe will be generally employed, all the more as the latest improvement of stereoscopic spectacles can be made at a very low price,[5] and therefore is accessible to all.

The change of form of the pupil is very distinctly visible on being examined with this loupe. I have examined such changes of form of the pupil very thoroughly in the Hospital of Prof. Charcot (Salpêtrière) in Paris, and the results of my researches were communicated by Prof. Brown-Séquard in the Parisian Academy of Sciences (1888). In cases of tabes dorsalis the pupil frequently appears oval and symmetrical in both eyes with a large and slanting diameter of the ellipse. These changes already take place in the beginning of tabes dorsalis and can be attributed to the nerve trouble of the vessels of the iris. The changes of form are not infrequently transitory (Buhmke).

Besides this there are other changes in the form of the pupil, which are caused by partial atrophy of the iris, appearing in consequence of functional troubles of the peripheric neuron. These changes of form take place at the later period of tabes dorsalis and are there stationary. The latter change of form of the pupil can be ascertained with the binocular loupe and is indicated by indistinctness of the irregularities of the surface of the iris, in the non-atrophied part of which protuberances and depressions are visible through the binocular loupe. These changes in the pupil likewise manifest themselves in cases of general paralysis (Talko).

By the aid of my stereoscopic magnifying lenses it is easy to ascertain the Argyll-Robertson symptom (pupilar contraction of convergence and the absence of these with impressions of light) and the

[2] Paris, Masson & Cie, editors, 1905.

[3] Encyclopedie Française d'Ophthalmologie, t. v., Paris, Doin & fils, 1905.

[4] Haltenhoff's de l'emploi en ophthalmologie de loupe binoculaire de Berger, La Clinique Ophthalmologique, 1905.

[5] By the optician Charles Hitchling, at Geneva, 29 quai des Bergnes, for the price of 7 francs. I hope that also in the United States the opticians will construct these stereoscopic spectacles, which are very useful for diamond cutters, watchmakers, miniaturists, naturalists, etc.

Gowers symptom, which precede the symptoms of Argyll-Robertson. The symptom of Gowers consists in oscillating movements of the iris in reaction toward light impression.

Many cases of tabes dorsalis in which examination with the naked eye leads to the conviction of the absence of pupillar reaction toward light has proved, when examined with the binocular loupe, that the pupil still showed tardy and passing contractions toward light impressions. It is likewise possible to recognize the symptom of Gowers by the use of the binocular loupe much earlier than with the naked eye. The binocular loupe is also very useful for the observation of the consensual reaction of the pupil toward light and the Pilez-reflex (pupillar movement by closing of eyelids).

I hope that this communication will contribute to awaken interest for further investigation of functional trouble of the pupil by means of the binocular loupe and so verify my researches, as also to perfect them by and through new researches.

EPIDEMIC CEREBROSPINAL MENINGITIS AT CAMP BEAUREGARD, LA.

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AND
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From November 10, 1917 to June 1, 1918, we had 126 cases of epidemic cerebrospinal meningitis, with 65 recoveries and 61 deaths, a mortality of 48.26 per cent. A review of these cases disclosed certain facts as to the transmission, forms of the disease, symptomatology, treatment and complications which may be of interest.

Transmission. Our experience leads us to believe that the patient, ill of the disease, as a disseminator of the infection is not dangerous, especially after active treatment has been instituted. Of many throat cultures taken upon admission and during the course of the disease, only one culture in one patient proved suspicious. Not one of the officers, nurses or enlisted men constantly in the wards during this period contracted the disease, although during November and December no precautionary measures, such as the wearing of masks or the use of sprays, were taken. The enlisted men particularly were careless in their handling of and close personal contact to patients. We have still to look upon the carrier as the dangerous agent to others only, for we have no record of any carrier who developed the disease.

FORMS AND SYMPTOMATOLOGY. Three forms of the disease were noted: the ordinary (frank and masked), the fulminating and the chronic forms. The ordinary form presented itself either as a frank meningitis with premonitory symptoms, as headache, loss of appetite, malaise and later chill, fever, vomiting, intense headache, painful stiffness in the muscles of the neck, great sensitiveness to noise, hyperesthesia, photophobia and the usual signs of meningitis, or as a masked meningitis with the symptoms-complex of influenza or laryngitis, chilly sensations, fever, general malaise, headache, pains in bones, hoarseness, cough, sore-throat, etc. This last form during the prevalence of influenza presented at first a perplexing problem, more easily solved later when a careful inspection for the typical petechial eruption very often present in these cases gave us a clue. One case, correctly diagnosed only on the third day of the disease, presented at the onset a typical picture of acute articular rheumatism. One symptom, noticed in most of these masked cases, never proved misleading, a "slow mentality;" patients were slow to answer questions, showed an aversion to being disturbed and wanted to be let alone. This symptom always justifies a lumbar puncture. A leukocyte count is always helpful and will often suggest the diagnosis. One of our first cases showing indefinite symptoms was correctly diagnosed before puncture upon a leukocytosis of 56,000.

The eruption in our experience has been helpful as a diagnostic point, being present in almost 50 per cent. of our cases as a whole, and in the last series, when carefully looked for, in 80 per cent. It appears first on the shoulders, forearms, legs and chest as petechiæ, erythema or rose-colored hyperemic spots in the ordinary form of the disease and as typical hemorrhagic spots of varying size in the fulminating forms or in very severe infections. We were so impressed with the value of this eruption as a diagnostic sign that it was our invariable rule to inspect carefully all patients presenting any suspicious symptoms. It was also noticed that these spots came on quickly, sometimes in a few hours, necessitating frequent inspections.

The fulminating form, of which we had 10 cases, proved how powerless we are in the face of this most dreadful disease. We include under this form only those cases which died within twenty-four hours of the onset. Five of these died within twelve hours. The onset was usually sudden, with violent chills, headache, great depression, fever, vomiting, slow, feeble pulse, hyperexcitability, followed by unconsciousness and delirium. Kernig's and later signs of the disease usually were not present. Two cases upon admission presented no definite symptoms and the disease was suspected only when unconsciousness supervened, a lumbar puncture in both yielding clear fluid under pressure with no organisms. Autopsy in both cases revealed only congestion of the meninges, a positive diagnosis being made on culture of the spinal fluid after death. One case lived six and a half and the other eight and a half hours after

the appearance of the first symptoms. Another case was brought in, showing profound depression and overwhelming intoxication, a hemorrhagic eruption appearing within three hours of the first symptom, quickly spreading over the whole body, with death in ten hours. Spinal fluid, clear, showed meningococci. Fluid and blood culture were both positive. The other cases presented no unusual symptoms except profound depression and a general expression of being acutely and desperately ill, with no improvement whatever under treatment.

We had 2 cases of the chronic form, the typical long-drawn-out cases of preserum days. One case, actively treated three times during the space of seventy-five days by the intraspinal, intravenous and intraventricular routes, finally died of hydrocephalus, due to blocking. It is but fair to state that the injection of serum into the lateral ventricles was done as a last resort. The other case recovered after a three months' siege of the disease.

Two cases developed a postmeningitic septicemia, both after an actively treated meningitis by the intravenous and intraspinal routes, blood cultures in the first case giving a meningococcus growth on the thirty-sixth day and the second on the sixteenth day of the disease. The first case had seven lumbar punctures, with 280 c.c. serum and three intravenous doses, 180 c.c. serum, ran a typical course until the nineteenth day, when the temperature, normal for five days, assumed an intermittent type, normal in the morning to 103° to 104° in the afternoon, after a daily chill, to return to normal in a few hours. The patient felt well between paroxysms and was up and about. Physical and blood examinations revealed nothing to account for the fever. On the thirty-fifth day a petechial eruption was noticed. On the thirty-sixth day a blood culture gave a meningococcus growth. The intravenous treatment was again instituted, the patient showing very severe anaphylactic reaction. On the forty-third day he developed an acute endocarditis. On the forty-seventh day blood culture was negative. On the sixtieth day the patient was well.

The second, another typical case, rather severe, did well under intravenous and intraspinal treatment up to the sixth day, when the temperature went up to 104.6°, developing physical signs of pneumonia, lobar. On the seventh day a blood culture gave a growth of pneumococci; a type differentiation, Avery's method, showed Type I. Antipneumococcic serum 100 c.c. intravenously on the seventh and again on the eighth day brought the temperature to normal, with general improvement in pneumonic condition. On the tenth day the temperature again went up to 105.6°, with cloudy spinal fluid. Blood cultures negative to pneumococci and meningococci. Active treatment, both routes, again instituted. On the twelfth day a blood culture again was negative. Temperature ran an up-and-down course, evening and morning, with the patient getting worse. On the

sixteenth day a hemorrhagic eruption appeared, quickly spreading over the whole body, particularly thick and marked on the hands, forearms, shoulders, face and legs, some spots being 2 cm. in diameter with a periarticular inflammation of the wrist and ankle-joints. Blood culture gave a meningococcus growth. Up to this day he had received 15 intraspinal doses of serum, 600 c.c., and 5 intravenous 300 c.c. Active treatment was continued up to the day of death, the twenty-first day, when, realizing the futility of these methods, an injection of 20 c.c. of serum into the lateral ventricles and the subdural space was resorted to as a last measure. It is rather difficult to offer any explanation of the blood-stream condition in these two patients after active treatment unless we theorize in the first case upon the flaring up of a latent focus of infection, and in the second the breaking loose of a walled-off focus never reached by the serum, reinfecting cerebrospinal system and the blood stream.

TREATMENT. It is not necessary at this day to argue and present statistics as to the value of serum treatment in epidemic cerebrospinal meningitis. It is conceded that a potent polyvalent serum, used in a systematic manner, is not only the accepted method of treatment but a specific. Major Flexner states that "the serum acts locally upon the meningococcus and upon the exudate, and in this way arrests the infection and promotes subsidence of the inflammation and restoration of the damaged membranes. To effect this it must be brought in direct relation and kept in continuous contact with the seat of the infection and in high concentration. Now, since the serum does not reach the meninges, normal, and less so the inflamed, from the blood, it is useless to inject it subcutaneously or intravenously in the expectation that it will find its way into the subarachnoid space."

Our experience has led us to the conclusion that the disease is a blood-stream infection, with local manifestations in the cerebrospinal system. The great percentage of cases showing the eruption when carefully looked for, 80 per cent. in the last series, and the great percentage of positive blood cultures when our laboratory facilities were adequate, forced us to this conclusion, and as a practical consideration we are justified in formulating our treatment upon such a theory. Therefore, to bring the serum in contact with the meningococcus, we use it in the blood stream, *i. e.*, intravenously, and in the subarachnoid space simultaneously. At the first puncture, unless there was positive evidence from the quantity, character and pressure of the cerebrospinal fluid that the disease was not epidemic cerebrospinal meningitis, 40 c.c. serum was administered after draining as much fluid as possible. If no untoward symptoms, such as intense headache, supervened the head of the bed was elevated to facilitate drainage. The serum was introduced by gravity only at an elevation of twelve to fifteen inches. Elevating the foot of the bed facilitated the introduction of the serum. The use of the

syringe and pressure was discarded altogether; 1 c.c. serum was then given subcutaneously for desensitizing purposes. In one to one and a half hours 60 c.c. serum diluted in an equal quantity of 0.6 per cent. saline solution was given intravenously. This was repeated every twenty-four hours for three doses unless some indications existed for its continuation. In severe infections 100 c.c. was given and repeated at closer intervals. In view of the fact that we had two cases of postmeningitic septicemia and several cases of blocking and reinfection from foci, and knowing that large doses of serum intravenously, repeated at frequent intervals, are well tolerated and practically harmless, we would recommend the larger dose at eighteen- or even twelve-hour intervals in all cases as a routine measure, in the hope of preventing these disastrous postmeningitic conditions and complications. The serum is not given with a view of reaching the subarachnoid space and acting locally upon the meningococcus in the cerebrospinal fluid, but to destroy the organisms in the blood and to prevent local complications in various organs, eyes, ears, heart, joints, etc. Lumbar puncture with a 40 c.c. dose of serum was repeated every twelve hours until the temperature reached normal. This was about the fifth or sixth puncture, at which time the fluid was generally clearing up. Lumbar puncture and the same dose of serum were repeated every twenty-four hours for a number of days, equal to one-half the number of punctures and serum injections it required to bring the temperature to normal, about three or four in the average case. The fluid was then found clear, with a predominance of lymphocytes in the cell count. Another spinal puncture was made in forty-eight hours and serum administered or not according to the appearance of the fluid and the general indications. On the fourth or fifth day after this last puncture another was made as a precautionary measure. In the average case the fluid was clear, with a slightly increased cell count, largely lymphocytes, and the patient convalescent. The temperature, after reaching normal about the fifth or sixth serum injection, often rose daily about four hours after each treatment. This rise is generally due to the serum, and in the management of our cases at this period we did not consider the temperature. Kernig's rigidity and retraction will in most cases be aggravated between the third and fifth day of treatment. As a rule this is due to the irritating action of the serum on the cerebrospinal system. Headache will also be more intense an hour or two after the serum injection. These signs and symptoms we generally neglected also, so that the management of our cases ultimately narrowed down to fluid findings.

From an analysis of fluid findings in many cases we have formulated the following, which represents the character of the fluid in the average case from day to day: At the first puncture the fluid may be clear, slightly cloudy, depending upon the duration or severity of the disease. Clear fluid in a positive case will show an increased

globulin content and a greatly increased cell count, mostly polynuclears and no organisms. This fluid will be cloudy on the second or, at the latest, the third puncture, when organisms may be found. If fluid is cloudy it will show many pus cells or leukocytes and generally organisms. These, however, may not be found on first puncture.

On second day: Fluid is more cloudy, contains more pus cells; organisms are generally found.

On third day: Fluid clearing up slightly and color changing to pale yellow or straw color; many polynuclear leukocytes staining well; no organisms as a rule.

On fourth day: Fluid clearing up, straw color; leukocytes, polynuclear, less abundant, staining well.

On fifth day: Fluid light straw color; few healthy leukocytes, polynuclears, some degenerating, poorly staining ones, and a few lymphocytes.

On sixth day: Fluid almost clear; few polynuclears and a preponderance of lymphocytes. In our experience, when the lymphocytes predominate in the cell count and the polynuclears show poorly staining qualities, the case is progressing satisfactorily and the twenty-four-hour puncture is discontinued.

To show the results of serum intravenously we have divided our cases into three series:

I. Those treated without serum intravenously, 83 cases, with 38 recoveries and 45 deaths; mortality, 54.2 per cent.

II. Those treated with serum intravenously late in the disease, 9 cases, with 4 recoveries and 5 deaths; mortality, 55.5 per cent.

III. Those treated intravenously on admission, 34 cases, with 23 recoveries and 11 deaths; mortality, 32.3 per cent.

Comparing figures in I and III shows the value of early intravenous treatment. However, comparison between I and II is not quite fair to the intravenous method for the reason that 8 of these 9 cases were very ill, almost hopeless, the method being used as a last resort. The fact that 4 of these cases recovered demonstrates the value of this procedure even late in the disease.

Other therapeutic measures: Hot baths, 112° to 115°, used in 39 cases, were found of distinct value to allay restlessness, clear up delirium and induce sleep. The duration of the baths was from five to fifteen minutes. Morphin hypodermically was used freely, and, in our opinion, is indispensable. The bromides, aspirin, sulphonal, trional, etc., were found absolutely useless. Bright light and noise were distinctly harmful and tended to make patients restless and wakeful. It was often noticed that when one patient in the ward became noisy, the others also soon became restless, irritable and noisy. One patient in series I, apparently in a dying condition, was tided over by a hot intravenous injection of 0.6 per cent. saline solution, 250 c.c., and ultimately recovered. The subsequent use of this measure in three other cases did not show such happy results.

Lumbar puncture in the first half of our cases was always done under chloroform anesthesia. Realizing the possible bad effect of the drug used once or twice daily over an extended period, we abandoned it for local anesthesia, subsequently used altogether except in the case of delirious and unmanageable patients. A 2 per cent. cocain solution, 0.5 c.c. under the skin, anesthetized it sufficiently to make the skin puncture painless. The ligaments and deeper tissues did not prove very sensitive in most patients, for very few complained of pain unless unusual difficulty was encountered in getting into the canal. Morphin sulphate, gr. $\frac{1}{4}$ hypodermically, was always given twenty minutes before a lumbar puncture under local anesthesia.

Four needles were broken, the accident occurring in delirious patients who became unmanageable, the needles already in the canal snapping off as the patients struggled to get away from the orderlies who held them.

Complications. All cases did not run a typical course. Some progressed satisfactorily up to the tenth, fifteenth or even twentieth day, when all symptoms reappeared, temperature, headache, vomiting, rigidity, retraction of the neck, irregularity or dilatation of pupils, slight occasional delirium, etc. Spinal fluid which had cleared up became cloudy again, with findings very similar to the first days of the disease and organisms. This occurred in cases having had active treatment and can be explained only by the breaking loose of a walled-off focus in some inaccessible place in the cerebral subarachnoid space, disseminating meningococci throughout the whole cerebrospinal system.

Blocking is another serious complication in the course of the disease. We understand by the term blocking the closing up by the exudate of the communication between the cerebral and spinal subarachnoid spaces at the base of the brain. This condition is generally due to one or more of three factors: insufficient treatment early in the disease; serum, in sufficient quantity, not reaching every portion of the subarachnoid space and ventricles, or treatment instituted late in the disease.

Blocking usually occurs late in the disease. It may, however, occur early, one of our cases blocking in forty-eight hours. This case presented an unusually severe infection. Symptoms may develop rapidly, as in this case, in six to eight hours, or may come on so gradually as to barely arouse suspicion until no fluid can be drained from the spinal canal. When the clinical picture of the disease does not improve under treatment it is well to be on guard. Headache, slow mentality, semicoma, delirium, vomiting, unequal pupils, nystagmus, early changes in retina and optic nerve suggestive of choked disk, a difference in note in auscultatory percussion of lateral ventricles, a gradually diminishing amount of cerebrospinal fluid changing from a pale yellow to a deep golden-yellow color, with few

cells, generally lymphocytes, and later a dry puncture, should establish a reasonably certain diagnosis.

In the presence of these complications the intraspinal and intravenous routes of medication offer very little hope of getting the serum in contact with the seat of the disease. The direct introduction of serum into the lateral ventricles and under the dura at the base of the brain is our only hope. Intraventricular puncture through a trephine opening in the skull was done in 5 cases, 3 of blocking and 2 for recrudescence, with 1 recovery, a case of blocking. This patient presented a severe form of the disease and had a rather stormy time under intraspinal and intravenous treatment until the eighteenth day, when temperature went up with aggravation of all symptoms, the spinal fluid diminishing in quantity and showing a deep yellow color. On the twenty-first day the patient had intense headache, was semidelirious, restless and generally worse; right eye showed marked internal strabismus; outlines of optic disk hazy; small bloodvessels of retina abnormally large and prominent; lumbar puncture dry. Up to this day the patient had received three intravenous, 180 c.c., and 18 lumbar punctures, 730 c.c. serum. On the twenty-second day lumbar puncture again dry. No improvement whatever. The left lateral ventricle was punctured through a trephine opening just below the left parietal eminence, some cloudy fluid drained and 10 c.c. serum was introduced in the ventricles and 10 c.c. under the dura. On the twenty-third day the general condition was the same: Left facial paralysis, right hemiplegia and aphonia. On the twenty-sixth day the patient was quiet and seemed to understand when spoken to. Intraventricular puncture through the same trephine opening, 45 c.c. clear fluid removed, 10 c.c. serum introduced. Fluid examination showed globulin double plus, considerable debris and some lymphocytes. On the thirtieth day the patient was able to move the right leg. On the thirty-first day, lumbar puncture, 70 c.c. clear fluid drained. Fluid examination showed a thin transparent coagulum, some debris and a few lymphocytes. No serum given. On the thirty-fifth day paralysis and aphonia had disappeared. Recovery thence uninterrupted. Our results, while not brilliant, are encouraging when we consider the gravity of the condition for which this operative procedure was undertaken.

Most of our cases developing these complications had an ample quantity of serum early in the disease, so that we are more inclined to consider the serum not reaching every portion of the subarachnoid and the cerebral ventricles as the responsible factor. Just why this condition should obtain in some cases we are unable to state, and so far having no means of determining this point early, it is our opinion that in very severe infections and in cases not progressing satisfactorily after a week or ten days of active treatment early intraventricular injection of serum is justifiable.

Serum reaction: We had 3 cases of very severe anaphylaxis, 2 in cases who had had serum three and five weeks previously, and 1 upon the first intravenous injection where the desensitizing 1 c.c. of serum was inadvertently omitted. The first symptom noticed was flushing of the face and chest, quickly spreading over the whole body, with sensation of heat, followed by choking sensation, dyspnea, restlessness, severe chill, unconsciousness, cessation of respiration, a fast weak pulse and later high temperature followed by profuse sweating. The condition of these patients was alarming but improved under adrenalin hypodermically and artificial respiration. One case of late serum sickness was interesting in that it presented symptoms very similar to postmeningitic septicemia, differentiated only upon a negative blood culture The case ran a typical course until the ninth day, when temperature, normal for three days, went up to 101° and a profuse general urticaria appeared over the whole body. Up to this day he had had seven lumbar punctures, 280 c.c., and three intravenous doses, 180 c.c. serum. On the seventh day spinal fluid was almost clear, with 60 per cent. lymphocytes. On the tenth day fluid was clear, showing nothing special. On the fourteenth day the eruption assumed a morbiliform appearance all over the body, less marked on the face, with intense itching and temperature of 102.4°. Spinal fluid clear. On the nineteenth day the eruption was distinctly hemorrhagic, the spots being the size of a split pea, with pain and swelling of the joints. Blood culture was negative. On the twenty-sixth day the skin was clear and the patient convalescing.

End-results. The end-results of our 65 cases discharged from the hospital as cured have not been very encouraging. Two were discharged on a surgeon's certificate of disability, one for manic-depressive insanity, existing prior to meningitis, the other for complete deafness, a sequel of the disease. Twenty-two cases now in the hospital, suffering from various pains and aches, stiffness of back, legs, etc., all classified as "postmeningitic neuroses," are apparently unable to do duty, and as far as we are able to determine at present will never be of much service. Of the remaining forty-one who are apparently well it is impossible yet to judge how many will be able to stand up under hard work, for it has been our experience that most cases did fairly well until put to the test of hard drills and long hikes. The severity of the disease does not seem to have any bearing upon the ultimate condition. The case of postmeningitic septicemia apparently is in as good condition as any other, full of energy, active, doing duty. One of the mildest cases who recovered under three punctures and two intravenous doses of serum is suffering as much as the case of blocking and intraventricular punctures. We are tempted to believe that there may be an element of malingering in some. We have seen what we designate as the "postlumbar puncture neurotic," in our opinion a malingerer. We have had in the

hospital three such patients, punctured once or twice as meningitic suspects, who complained as much as the chronic case who had a three months' siege of the disease with twenty-five lumbar punctures. The true evaluation of the malingering element is the problem which confronts us now. However, we have no doubt that the majority really suffer and are disabled, although with our present means of diagnosis we are unable to detect any pathological lesions to account for their condition.

The work here reported was done in the service of Major James B. Guthrie, and we desire to thank him for allowing us to analyze it. Credit should be given to the following officers: Captains Ward, Dorsett and Steele and Lieutenants Zuercha, Ruka, Sharp and Bell, who were connected with the service and carried on the care and treatment with the compilers of this report.

INFLUENZA–PNEUMONIA CASES SHOWING GAS IN FASCIAL TISSUES.[1]

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During the epidemic of influenza-pneumonia at Camp Dix a number of cases have shown peculiar accumulation of gas in the fascial tissues. Twelve such cases have been studied as closely as the exigencies of a crowded service would permit. Three of the cases have recovered. A total of twenty were reported.

Gas first made its appearance in the subcutaneous tissue at the base of the neck anteriorly and laterally and over the upper portion of the chest, from the clavicle to about the third rib. While this was the usual location two cases have shown a more extensive distribution of gas. In one case gas was found also in the subcutaneous tissue of the cheeks, eyelids, mesial aspect of the entire right arm and in small areas over the sides of the chest and abdomen and in the flanks.

During life the patients showed a slight ballooning of the skin over the affected areas. These areas were distinctly crepitant, the gas disappearing from the immediate region of the palpating finger on pressure. A notable feature is that the skin over the ballooned area

[1] Extract from a paper read before a meeting of the Medical Society of the County of Kings, Brooklyn, N. Y., October 15, 1918.

felt cold to the touch while the neighboring tissues were feverish. There was no perceptible change in color of the tissues in the affected areas.

The patients with this accumulation of gas have shown no related subjective symptoms, and no symptoms of an intercurrent infection. There has been no discoloration of the affected areas. No edema, no congestion and no induration or other signs of infection have been observed. It has not been associated with any other especially characteristic symptoms or physical signs. The accumulation of gas has apparently not affected the course of the disease. It appears to be an inert gas in the tissue spaces. The affected tissues gave a crackling sound on pressure with the stethoscope. In one case, Lieutenant John J. Young, M. C., of Ward No. 37, records "over the precordium rales very similar to sounds elicited with moderate pressure of stethoscope over emphysematous cutaneous tissue." At autopsy the mediastinal connective tissue was distended with gas in this case.

Postmortem Findings. Three of the cases described have come to autopsy. The pathological findings were not those of cases dead of infection with Bacillus aërogenes capsulatus, nor in fact did the lesions present the characteristics of an infection.

In the three subjects which came to autopsy the distribution of the gas has likewise varied in extent. In the most pronounced case the gas was distributed in the subcutaneous fascia as follows: over the upper anterior portion of the chest as far laterally as the axilla, continuing upward over the front of the neck and laterally as far as the anterior border of the trapezius muscle, over the parotid region, over both cheek areas and eyelids. Similarly it could be felt in the vascular sheaths of the right axillary, brachial and radial arteries as far as the base of the thumb. Within the chest the fascia of the anterior and posterior mediastinum appeared as a reticular tissue distended with gas and bearing more or less fatty tissue. Gas was also found beneath the pleura at the hilum of the lung and in the smaller septa of the lung. In the last-named situation small gas vesicles were seen especially frequently at the edges of the small septa passing inward from these. In no case was gas observed within the muscle sheaths, and the muscles were firm and normal in appearance.

On section the superficial gas-containing fascia of the neck appeared distinctly whitish. The bloodvessels appeared to contain less blood than those elsewhere. There was no discoloration, no fluid, no infiltration or other signs of pathological change. There was no particular odor to the affected tissue and neither the liver nor any other internal organ gave any evidence of gas accumulation.

Bacteriology. Small bits of the gas-containing fascia were removed for inoculation on various solid and liquid media. These were incubated both aërobically and anaërobically. In no case was

a growth obtained. No bacteria were found in the smears made directly from the excised and crushed gas-containing tissue.

SUMMARY. 1. Those cases of influenza-pneumonia at Camp Dix which showed gas in various fasciæ showed clinically no evidence of an intercurrent infection.

2. Three gas cases ran an uneventful course and recovered without surgical procedure.

3. At autopsy the gas-containing tissue showed little blood in the vessels. It presented no discoloration, no congestion, no induration or other signs of inflammation.

4. Bacteria were not recovered.

5. Gas was not found within the muscle sheaths.

6. In the gas cases coming to autopsy the air-containing alveolæ appeared emphysematous in the more nearly consolidated lung lobes.

7. The distribution of the gas corresponds with what we would expect to be the dissemination of gas escaping from the weakened alveolæ of the lung under pressure.

8. We are of the opinion that the "gas" in the above cases of pneumonia is air from the lung which reaches its distribution as a result of purely mechanical factors. We do not believe the gas is of bacterial origin.

RENAL DIABETES.[1]

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THAT diabetes is not always a rapidly fatal disease has long been recognized by medical writers, the diagnosis being founded upon the chief sign of the disease, the persistent presence of sugar in the urine. In many cases this is the only symptom, the patients enjoy excellent health, the glycosuria persists and seems to be little influenced by diet, and, after years under observation, may remain unchanged or may entirely disappear. The association of the kidneys with the etiology of diabetes is not to be wondered at, especially from the 17th century, when Thomas Willis discovered that the pathological change in the urine was the presence of sugar, and Dobson, in 1775, demonstrated that the blood contained sugar before it appeared in the urine. One naturally conceived of a permeability point in the concentration of blood sugar at which the

[1] Read in part before the Society for Experimental Biology and Medicine, May 17, 1916, Proceedings, xiii, 153.

kidney tolerance would be overcome and sugar would escape into the urine. In the ordinary cases of diabetes it was observed that the urine sugar varied more or less directly with the diet and the patient's tolerance was estimated by the amount of carbohydrate that could be ingested without producing glycosuria. The question arose whether one was dealing with a condition in which this permeability point was lowered by organic or functional kidney changes or whether the kidneys were unaffected and the symptoms due to a constitutional defect in carbohydrate metabolism. Early writers, as Galen, Aetius of Amida and others, considered it to be a kidney disease. Theophrastus Patrocelsus, however, described it as a constitutional disease showing itself in marked pathological changes in the urine. In 1878 Claude Bernard,[2] by very imperfect methods, demonstrated that an excess of sugar in the blood was the direct cause of glycosuria.

Von Mering's[3] demonstration of phlorizin glycosuria in 1886 raised the question as to whether a like condition occurred clinically in man, a state in which the kidney permeability point to sugar was so lowered that glucose appeared in the urine in the presence of a subnormal or normal blood sugar. In 1896, Klemperer[4] reported a case which he styled "Renal Diabetes" and stipulated that for such a diagnosis one must have the following postulates fulfilled:

I. That the glycosuria should be within wide limits independent of the amount of carbohydrate in the food.

II. That the sugar in the blood should at least not be increased but should rather be diminished.

III. That the development of a nephritis decreases the glycosuria.

Schupfer,[5] in criticism, pointed out the fact that although a complicating nephritis usually causes a lessening or cessation of a mild glycosuria, in other cases no change can be found and claimed this to be the case in arteriosclerosis complicating diabetes. Lüthje[6] in 1901 claimed that in order to make the diagnosis one must ascertain that the glycosuria develops as a direct result of a nephritis, that the blood sugar be below normal and that no relation exists between the blood sugar and the extent of the glycosuria. In 1908 Bonniger[7] questioned the diagnosis made in all previous cases as the blood sugar estimations were based upon the reducing power of whole blood. This, he said, gave us erroneous values as he was under the impression that blood corpuscles contained very little sugar. Tachau[8] further decorated the diagnostic requisites by

[2] Leçons sur le diabète, Paris, 1878, 75.
[3] Verhandl. d. Cong. inn. Med., Wiesbaden, 1886, v, 185.
[4] Verein f. innere Med., Berlin, 18 Mai, 1896.
[5] Il Policlinico, 1900, vii-m, 1.
[6] München. med. Wchnschr., 1901, xlviii, 1471.
[7] Deutsch. med. Wchnschr., 1908, xxxiv, 780. Verhand. d. Cong. f. inn. Med., 1913, xxx, 178.
[8] Deutsch. Arch. f. klin. Med., 1911, civ, 448.

stipulating that the glycosuria, in addition to being completely or in a great degree independent of the diet, must persist upon a diet free from carbohydrates and that it be not greatly increased, following the ingestion of large amounts of sugar.

Von Noorden[9] claimed that blood sugar estimations must be the deciding factor, and in this connection, Frank,[10] in 1910, again brought up Bonniger's criticism of whole-blood estimations. Jacobsen,[11] in 1913, published some very interesting data on alimentary hyperglycemia and glycosuria. He found that one hour following the administration of 100 grams of glucose the hyperglycemia had passed off in most of the cases examined and the blood sugar test at this time showed only a very slight increase. He pointed out that this is probably what happened in the cases diagnosed as renal diabetes.

De Langer,[12] in 1914, stated that to make a diagnosis of renal diabetes the glycosuria need not be uninfluenced by the diet and pointed out that in phlorizin diabetes the urine sugar is greatly influenced by ingested carbohydrates.

Galambos,[13] in the same year, differentiated between mild diabetes mellitus and renal diabetes as follows: "When a chronic glycosuria is present with but a questionable or no hyperglycemia, we have to do with either a diabetes mellitus with increased kidney permeability or with renal diabetes. When the blood sugar is slightly increased the case is one of diabetes mellitus with increased renal permeability. When, however, the blood sugar is subnormal or normal, or when alimentary hyperglycemia is absent, the case is one of renal diabetes. "Glycosuria largely independent of the diet speaks for renal diabetes."

Salomon,[14] also in 1914, cited the work of Porges, Leindorfen and Stresower and Frank as showing that an independent glycosuria with low blood sugar values can exist in patients showing no sign of kidney disease. He stated that renal diabetics excrete small amounts of sugar daily, 10 to 12 grams, and that this is uninfluenced by diet; also that 100 grams of glucose in the morning do not increase the sugar excretion.

The consensus of opinion seems to have been that renal diabetes was a condition in which the patient had none of the classical symptoms of diabetes mellitus but did have a low-grade glycosuria, little influenced by diet, and which was present at a time when the blood sugar was normal. In view of the fact that Lewis and Mosenthal[15] have but recently given an excellent review of the cases so far reported a repetition would seem out of place at this time.

[9] Die Zuckerkrankheit., Berlin, 1912, 527.
[10] Arch. f. exper. Pathol. u. Pharmakol., 1913, lxxii, 387.
[11] Biochem. Ztschr., 1913, lvi, 471.
[12] Berlin klin. Wchnschr., 1914, li, 1792.
[13] Deutsch. med. Wchnschr., 1914, xl, 1301.
[14] Ibid., xl, 217.
[15] Johns Hopkins Hosp. Bull., 1916, xxvii, 133.

In reviewing the cases, however, one is impressed by the fact that most of the diagnoses were based upon the observations that the patients had no diabetic symptoms and that the glycosuria seemed to bear no relation to the diet. When it came to actually determining the point of permeability to sugar and whether or not sugar was escaping from the kidney at the very time when the blood sugar was normal, little can be found to establish the diagnosis.

The case described by Gram[16] had a low glycosuria of from 0.4 to 0.6 per cent. at the time when synchronous specimens of blood contained 0.085 to 0.1 per cent. sugar. Lewis and Mosenthal[14] reported a case with a constant glycosuria in twenty-four-hour specimens, during a period of five days' starvation; blood tests made on the third and fifth days gave normal values (0.11 per cent.). The patient had no diabetic symptoms. We cannot draw conclusions from their synchronous blood and two-hour urine tests. The blood specimens were taken at a time when alimentary hyperglycemia had passed off, but the urine at that time would still normally have sugar as a result of the hyperglycemia.[17] Other blood specimens were taken just before eating and the synchronous urine specimens contained the alimentary glycosuria of from one to two hours.

Murlin and Niles[18] have described a case which they consider to be one of renal glycosuria. The patient, a man, aged twenty years, suffered from loss of weight, furuncles, polyuria, increased thirst and weakness. The daily excretion of glucose varied from 14.7 to 26.9 grams and bore no relation to the carbohydrate content of the diet, which varied from 14.9 to 100 grams. The blood-sugar estimations were made five hours after breakfast and gave normal values on several days. One day's starvation rendered the urine sugar-free. No synchronous blood and urine tests were made and nothing is known of the permeability point to sugar or of the nature or extent of alimentary hyperglycemia and glycosuria. The blood sugar findings are such as one would expect in mild diabetes.

The above case reported by Gram is certainly one of "glycosuria with normal glycemia," as Allen states it. Several other cases, including that of Lewis and Mosenthal and that of Bonniger, seem to approach this type, but the data from which to draw conclusions are insufficient. It is known that the blood sugar level when uninfluenced by diet or by glycogenolysis varies in different individuals, high levels being found in diabetes of long standing and in nephritis. So it would be quite possible for a nephritic whose blood sugar level is above 0.2 per cent. to have a glycosuria of renal origin which would not be dependent upon an increase of blood sugar in that individual. One of the cases about to be reported is of this type.

The value of the blood sugar method has frequently been brought

[16] Hospitalstidende, Copenhagen, 1915, lviii, 329.
[17] Frank: Ztschr. f. physiol. Chem., 1910, lxx, s. 129.
[18] Am. Jour. Sc., 1917, cliii, 79.

into question in deciding the type of the case. Bonniger's and Frank's criticism of whole blood estimations is not without foundation, as the sugar concentration of the plasma alone must be the deciding factor influencing the kidney cells. However, in the light of recent work,[19] this would tend to include more cases as renal glycosuria, since the corpuscles seem to have, as a rule, a slightly greater concentration of sugar than the plasma.

The following cases are reported as showing two distinctly different types of glycosuria which seem to be of renal origin. The blood sugar estimations were made by a modification of the Lewis and Benedict method already described.[20]

CASE I.—Mrs. M. B., an American housewife, aged thirty-one years, was admitted to the service of Dr. Quintard in the New York Post-Graduate Hospital on July 30, 1915. Case History No. 5356. She was sent to the hospital on account of an intractable glycosuria complicating pregnancy.

Family History. Mother died of "inflammation of the bowels." Father, aged seventy-four years, living and in good health. Two brothers and four sisters are living and in good health. Her family have all been of an extremely nervous temperament. No history of diabetes, obesity, gout, goitre, tuberculosis, gigantism or disorders of the kidneys, stomach or heart.

Personal History. Born in Westminster, Vermont, of old New England stock. She experienced poor health from early infancy and has always been poorly nourished. Her mother told her that when a child the urine was irritating, and that only by the best of care could the vulva be kept in a healthy condition. From early childhood she has had a weak stomach and suffered from severe attacks of indigestion. These attacks were usually accompanied by marked urticaria, especially so following the ingestion of fish. She has a peculiar susceptibility to the sting of the honey-bee. On one occasion, four years ago, she almost died from the effects of a sting. It was followed by nausea, vomiting, purging, loss of consciousness, marked edema and extreme weakness of pulse. Brisk stimulation brought about recovery in a few hours. Had chicken-pox when a child; catarrhal jaundice at the age of thirteen; normal menstruation began at fourteen; mumps when eighteen. Married at the age of twenty-three and two months later had a second attack of catarrhal jaundice. Her first child was born one and a half years after marriage. Early in the pregnancy she noticed burning, frequency and urgency of urination. Her physician found sugar in her urine and made a diagnoss of diabetes mellitus. Before this date (1908) her urine had never been tested for sugar.

History of Present Illness. Following the discovery of the glycosuria she was placed upon a restricted diet, but as this was followed

[19] C. V. Bailey: Proc. Soc. Exper. Biol. and Med., 1916, xiii, 153.
[20] Myers and Bailey: Jour. Biol. Chem., 1916, xxix, 147.

by a rapid loss of weight and extreme weakness it was soon abandoned. The patient returned to her usual diet and quickly regained both weight and strength. After two weeks the urine was again examined for sugar, which was present to the extent of 5 per cent., or about the same amount as before the restricted dieting. This glycosuria persisted throughout the pregnancy, which was otherwise uneventful. Her diet continued unrestricted, her weight increased to 150 pounds and she looked and felt in perfect condition. A baby girl, weighing ten and a half pounds, was delivered under ether anesthesia. An endometritis lasting three weeks followed the birth of this child. Recovery was good, and since that time the patient has been in fair health.

Four years ago another unsuccessful attempt was made to render her urine sugar-free, but was quickly abandoned, due to rapid loss of weight and extreme weakness. Since that time her diet has been unrestricted. Her appetite has always been good—never abnormal. She has not had increased thirst. The urine volume has been about 1500 c.c. She has had a distaste for sweet things, but is fond of fruit. She has always been undernourished, nervous and rather easily exhausted, but has been able to do all the housework for three adults and a child. In the past seven years there have been no subjective urinary symptoms. Her chief complaint has been of occasional attacks of indigestion, when she would suffer from headache, nausea, vomiting and epigastric distress. No hematemesis. Bowels regular. No constipation. Diarrhea at times. No blood or excess of fat in the stools. Menstruated regularly up to three months ago.

Physical Examination. Poorly nourished, symmetrical adult female of rather querulous temperament. The skin is very transparent; cheeks flushed; lips very red; veins of neck, chest and temples prominent; eyelashes long; slight seborrhea of scalp; pupils equal, regular and react well to light and accommodation; no exophthalmos; no widening of palpebral fissures; von Graefe's sign negative; corneal sensibility slightly decreased; upper and lower teeth missing; mucous membrane bright red; throat apparently normal; thyroid gland slightly enlarged, symmetrical and does not pulsate; no tremor of extended fingers; reflexes all present and active; no swaying on standing with feet together; no ataxia; chest symmetrical, subcostal angle acute, expansion equal and good; breasts enlarged, slightly tender and areolæ pigmented; examination of lungs reveals nothing abnormal; cardiac dulness extends to right sternal border; apex beat palpable in fifth intercostal space in midclavicular line; heart sounds normal—no adventitious sounds; arteries barely palpable; pulse 84, regular and equal; blood-pressure: systolic 110, diastolic 65; respirations 22; temperature normal; abdomen enteroptotic and flatulent; liver palpable at costal margin; upper pole of right kidney can be palpated; spleen not enlarged; bimanual examination reveals an enlarged uterus;

no abdominal tenderness or abnormal masses are present; no edema of extremities; hemoglobin 68 per cent. (Sahli); red blood cells 4,444,000; leukocytes 7900, of which 64 per cent. are polymorphonuclear; urine light straw colored—specific gravity 1047—and shows a slight trace of protein, acetone and diacetic acid, and sugar 5 per cent.; microscopically—a few hyaline and granular casts; phenolsulphonephthalein excretion on August 10, 1915, was 39 per cent. in two hours; on August 17 the excretion was 42 per cent. in two hours.

On August 3, 1915, her blood in the morning before breakfast showed 0.09 per cent. sugar, and the urine at the same time contained 1 per cent. sugar. A comparison of the blood and synchronous urine sugar is found in Table I, Case I. The effect of starvation upon her weight and excretion of sugar is shown in Table II, Case I, the patient at the same time being at rest in bed.

TABLE I.—CASE I.

Date.	Blood sugar. Per cent.	Synchronous urine sugar. Per cent.
Aug. 3, 1915	0.089	1.00
Aug. 5, 1915	0.110	1.60
Aug. 6, 1915	0.130	2.10
Aug. 11, 1915	0.098	3.10
Aug. 25, 1915	0.092	1.25
Oct. 13, 1916	0.116	8.40

This table simply shows that with normal blood-sugar values, sugar was constantly excreted by the kidneys. As the rate of excretion of urine is not known the relationship of sugar excretion to blood-sugar concentration cannot be expressed.

TABLE II.—CASE I.

Date.	Diet.	Weight. Pounds.	Glucose excreted. Grams in twenty-four hours.
Aug. 3, 1915	Regular	103	35.0
Aug. 5, 1915	Hunger	99	18.3
Aug. 6, 1915	"	96	14.7
Aug. 7, 1915	"	95	19.5

Test of Alimentary Hyperglycemia and Glycosuria. On the morning of August 11, 1915, synchronous blood and urine specimens were obtained, the patient being in the fasting state. She was then given 30 grams of glucose in 225 c.c. weak tea. Blood and urine specimens were obtained at frequent intervals for a period of six hours. The results are tabulated in Table III, Case I, and in Chart I, Case I.

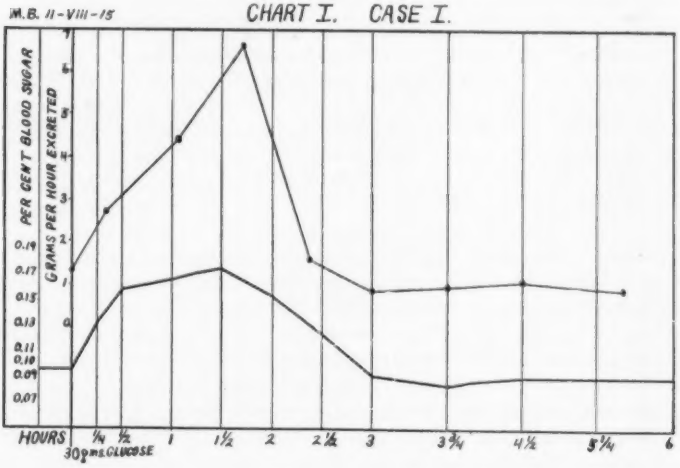
It will be seen that the patient excreted glucose at the rate of 1.29 grams per hour when the blood contained 0.098 per cent. sugar. Alimentary hyperglycemia was slightly delayed and prolonged, as is found in mild cases of nephritis. Urinary excretion greatly increased on the subsidence of the hyperglycemia.

The greatly increased permeability of the kidneys to sugar is well shown at the one and a half hour period, when the rate of glucose excretion was 6.7 grams per hour while the blood sugar was at a point where normal kidneys just become permeable.

TABLE III.—CASE I.

M. B., August 11, 1915.

Time.		Blood sugar. Per cent.	Urine.				Fluid intake. c.c.
A.M.			c.c. per hour.	Chlorides. Grams per hour.	Sugar.		
					Per cent.	Grams per hour.	
9.15	....	0.098	60.0	0.0460	3.120	2.000	
9.45	....	30 grams glucose.	44.0	.....	2.940	1.290	225
10.00	½ hr.	0.135					
10.20	½ hr.	0.159	58.0	0.1056	4.830	2.830	225
10.30							
10.45	1 hr.	0.168	.....	.....	.....	.....	225
11.00	1½ hrs.	0.172	66.0	0.1450	6.660	4.398	
11.10							
11.15	1½ hrs.	0.176					
11.45	2 hrs.	0.156	97.0	0.2180	6.750	6.700	225
12.15	2½ hrs.	0.105					
12.25	....	.....	159.0	0.2540	1.040	1.650	
12.45	3 hrs.	0.093					
1 P.M.	....	.....	94.0	0.1690	0.952	0.897	
1.25	3½ hrs.	0.086					
1.45	4 hrs.	0.088	150.0	0.2100	0.657	0.986	225
2.00							
2.15	4½ hrs.	0.092					
3.00	5½ hrs.	0.092	90.0	0.1400	1.219	1.097	
3.45	6 hrs.	0.092	84.0	0.1340	1.086	0.912	225



The patient was put upon a mixed diet containing about 50 grams of available carbohydrate. Upon this diet her twenty-four-hour urine contained not more than 2 per cent. glucose while her normal weight was sustained. Her freedom from unpleasant symptoms, however, prompted her to return to unrestricted diet upon leaving

the hospital on August 25. In two weeks her weight increased twenty pounds. The second pregnancy was uneventful, and on January 28, 1916, she was delivered of a healthy baby weighing nine pounds, nine ounces. Glucose was constantly present in the urine.

In October, 1916, nine months after the birth of her second child, further tests in alimentary hyperglycemia and glycosuria were carried out. At this time the percentage glucose in her daily urine had greatly increased, being 7.4 per cent. on October 15, 6.94 per cent. on October 16, and 9.2 per cent. on October 17. On the morning of October 13, synchronous blood and urine specimens were obtained, the patient being in the fasting state. She was then given 30 grams of glucose in 400 c.c. of weak tea. Blood and urine specimens were obtained at frequent intervals for the succeeding six hours. The results are shown in Table IV, Case I, and Chart II, Case I.

The initial blood sugar value was within normal limits, but at the time sugar was being excreted by the kidneys at the rate of 2.98 grams per hour.

The blood sugar curve reached its highest point in one hour and returned to its original value in two and a half hours, as is normally the case. The rate of sugar excretion increased with the blood sugar, so that when the latter was at a concentration of 0.189 per cent., sugar was being excreted at the enormous rate of 9.9 grams per hour. (A comparison of the rate of fluid excretion with the concentration of sugar in the blood is interesting, as during the rapidly developing hyperglycemia the fluid excretion dropped off markedly and then quickly increased as the kidneys rapidly removed the excess of sugar from the blood. This decreased excretion occurred in spite of the fact that 400 c.c. of fluid were imbibed with the glucose.)

If we compare the findings at this time with those of the similar test taken fourteen months previous (at which time the patient was four months pregnant) we notice that the blood sugar in the fasting state has increased to the normal value. This, however, is easily explained, as the tests in August, 1915, were made following three days of fasting, while the latter tests followed but a ten-hour fast. The excretory power of the kidneys for glucose has increased, and the more rapid rise of blood sugar following the ingestion of glucose probably indicates an increase in absorptive power of the intestines.

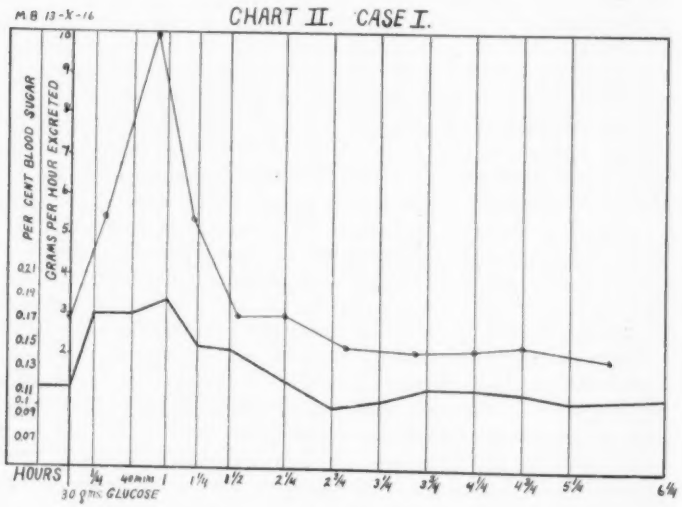
The general condition of the patient was unchanged. Her chief complaint was lack of reserve energy. This was most distressing upon restricting the diet. The urine sugar remained above 6 per cent. in the twenty-four-hour specimens.

The patient was again examined on December 20, 1917. Her physical condition remained unchanged. She stated that for the preceding fourteen months her health had been excellent, her only complaint being lack of reserve energy. Her diet was unrestricted. Examination of a twenty-four-hour urine specimen on November 4, 1918, showed an excretion of 1440 c.c.; specific gravity 1040; sugar 4.5 per cent.; albumin negative.

TABLE IV.—CASE I.

M. B., October 13, 1916.

Time.		Blood.		Urine.			Fluid intake. c.c.
A.M.		Hemoglobin. Units.	Sugar. Per cent.	c.c. per hour.	Sugar. Per cent.	Sugar. Grams per hour.	
9.15	....	67	0.116	63.0	8.3	2.98	
9.30	....	30 grams glucose.	.....	.....	.....	.....	400
9.45	¼ hr.	62	0.177				
10.10	¾ hr.	61	0.177	36.0	11.9	5.35	
10.30	1 hr.	62	0.189				
10.40	....	.....	.....	45.0	3.0	9.90	
10.50	1¼ hrs.	63	0.150				
11.00	....	.....	.....	33.0	1.6	5.28	
11.10	1¾ hrs.	64	0.147				
11.30	....	.....	.....	80.0	3.7	2.96	
11.45	2¼ hrs.	65	0.120	120.0	2.5	3.00	
12 M.							
12.15	2¾ hrs.	65	0.100	37.0	6.2	2.31	
12.45	3¼ hrs.	66	0.106				
1.15	3¾ hrs.	67	0.116				
1.30	....	.....	.....	56.0	5.6	2.09	
1.45	4¼ hrs.	67	0.114				
2 P.M.	....	.....	.....	36.0	6.0	2.16	
2.15	4¾ hrs.	67	0.112				
2.30	....	.....	.....	34.0	6.5	2.21	
2.45	5¼ hrs.	68	0.106				
3.30	....	.....	.....	28.0	6.8	1.90	
3.45	6¼ hrs.	68	0.108				



SUMMARY. The case reported is one of constant glycosuria without hyperglycemia. Alimentary hyperglycemia while the patient

was pregnant was slightly delayed and prolonged, this being probably due to decreased functional activity of the bowels and kidneys. Alimentary hyperglycemia in the non-pregnant state was of the normal type,[18] the curve reaching its highest point in about one hour, returning to the original value in two and a half hours, falling to a lower point in three hours, then increasing and maintaining its level in three and a half to four hours' time. Alimentary glycosuria was excessive. It varied directly with the glycemia and was present to a marked degree even in the presence of a hypoglycemia, the permeable point of the kidneys being below a blood sugar concentration of 0.086 per cent. (the normal kidneys being permeable between 0.16 and 0.17 per cent.). The patient's history points strongly to this being a congenital condition.

Since the accidental discovery of sugar in her urine in 1908 her condition has remained unchanged, although her diet has never been restricted. Her daily output of sugar is about 20 grams.

Case II.—J. E. P., English-American, aged sixty-two years, a toolmaker by trade, was admitted to the New York Post-Graduate Hospital, to the service of Dr. Quintard, on August 25, 1915. Case History No. 5940. He complained of swelling of the feet and abdomen and shortness of breath.

Family History. Mother died at seventy-six, cause unknown; father died at thirty-nine, cause unknown. Three brothers and three sisters are alive and well. No history of obesity, diabetes, nephritis, gout, goitre, tuberculosis, rheumatism or heart disease.

Personal History. Born in England of English parentage. Came to the United States when a young man. With the exception of a gall-bladder disturbance, for which he was operated upon thirteen years ago, he has enjoyed good health up to the onset of his present illness. He has no knowledge of disease in childhood and denies having had venereal disease. He was married twice; the first wife bore eleven healthy children and no miscarriages; the second wife is alive and in good health.

Habits. Alcohol in moderation. For years he has used tobacco to excess and has been a heavy meat-eater. He has never engaged in dangerous occupations.

History of Present Illness. Dates back two years, when he noticed dizziness, spots before the eyes, failing vision and severe headaches. Six months later he noticed a puffiness under the eyes and swelling of the feet and legs. These symptoms gradually increased in severity and three months ago he developed dyspnea on slight exertion, and the necessity of urinating at least once at night. Shortly before coming to the hospital he became very restless and orthopneic. His appetite has always been good, never ravenous; bowels regular; never jaundiced; no blood in stools; no nausea or vomiting; no gastric disturbances, cough or hemoptysis. His daily output of urine has not been increased. He has had none of the symptoms

associated with diabetes (polyphagia, polydypsia, polyuria, obesity, emaciation, skin lesions, pruritus or neuritides); no symptoms of disturbance of the hypophysis, thyroid, pancreas or adrenals. He has no knowledge of having passed sugar in his urine.

Physical Examination. Well-developed and well-nourished male. Height 5 feet 6 inches; weight 198½ pounds, lying in dorsal position moderately dyspneic; marked generalized edema, especially of feet, legs, thighs, scrotum and hands; abdomen pendulous and edematous; slight cyanosis of ears, nose and lips; skin dry, scaly and transparent; soft edema about eyes; sclera clear, pupils equal, regular in outline and react well to light and accommodation; von Graefe's sign absent; no exophthalmos; no widening of palpable fissure; tongue coated; teeth decayed; marked pyorrhea; nothing abnormal found in nose or throat; veins of the neck engorged; thyroid palpable but not enlarged or pulsating; thorax emphysematous and symmetrical; expansion poor; respirations shallow; moist rales heard over base of lungs and free fluid can be demonstrated in the pleural cavities; temperature 98°; pulse 84; respirations 22; pulse irregular and unequal; arteries hypertrophied; apex beat diffuse and heaving; no thrill over precordium; area of cardiac dulness 3 cm. to right and 12 cm. to left of midsternal line; aortic second sound accentuated; no adventitious sounds; blood-pressure: systolic 190; diastolic 130; marked edema of abdominal walls; old scar in region of gall-bladder; moderate ascites; a small indirect inguinal hernia on right side just emerges from the external ring but does not descend into the scrotum; on the left side is a small hernia just reaching the external ring; scrotum very edematous and the tunica vaginalis on the right side distended with fluid; liver, kidneys and spleen not palpable; reflexes (abdominal cremasteric, knee-jerk, ankle-jerk, etc.) all present and active; no ataxia; Rhomberg negative; skin shows a dark brown pigmentation over the lower chest and the upper abdomen; dry, scaly eczema over both tibiæ.

The fundus of the right eye shows an angiopathic neuroretinitis, with numerous areas of fatty degeneration in macular region and numerous flame-shaped hemorrhages along the vessels near the disks. The left eye shows a cloudy vitreous with large floating bodies occluding the view of the fundus.

Volume of twenty-four-hour specimen of urine 625 c.c.; color dark amber; specific gravity 1025; dry protein per liter 3.1 grams; sugar 0.6 per cent.; total chlorines as NaCl 6.6. grams; acetone negative; diacetic acid negative; many hyaline and granular casts; phenolsulphonephthalein excreted 8 per cent. in two hours.

An examination of the blood shows 83 per cent. hemoglobin; 4,592,000 erythrocytes; 12,400 leukocytes, of which 74 per cent. are polymorphonuclears and 23 per cent. lymphocytes.

Complement-fixation test for syphilis negative. Chemical blood analysis during fasting showed blood sugar 0.18 per cent.; chlorides

as NaCl 0.73 per cent.; urea nitrogen 23 mg. per 100 c.c. blood; uric acid 4.0 mg. per 100 c.c. blood; creatin 7.4 mg. per 100 c.c. blood; creatinin 1.9 mg. per 100 c.c. blood.

Subsequent History. The patient remained in the hospital ten months and underwent ordinary treatment for chronic parenchymatous nephritis. At times he showed marked improvement, followed by relapses, and finally died on June 1, 1916. During his stay in the hospital his urine was never free from sugar, the percentage remaining in the neighborhood of 0.5 per cent., varying slightly inversely with the volume and seemingly independent of the diet.

Test of Alimentary Hyperglycemia and Glycosuria. On the morning of December 13, 1915, before the patient had anything to eat or drink, specimens of his blood and urine were obtained. He was then given 33 grams glucose in 250 c.c. of weak tea, and specimens of blood and urine were obtained as frequently as possible for the succeeding five and a quarter hours. The findings are recorded in Table V, Case II, and Chart I, Case II.

It will be noticed that the initial blood sugar value is that commonly met with in cases of severe nephritis.[21] The urine, however, contained 0.52 per cent. glucose, the excretion being at the rate of 0.22 gram per hour. Alimentary hyperglycemia was delayed, reaching its maximum in one and a half hours and not returning to normal until four and a quarter hours had elapsed. The rate of urinary excretion decreased and was uninfluenced by the fluid intake. The rate of sugar excretion varied directly with the excretion of urine and bore no relation to the concentration of sugar in the blood. The blood volume, as indicated by the hemoglobin, showed a slight increase at the onset of the hyperglycemia, but returned to the original value in one and a half hours.

On March 11, 1916, the test was repeated, using on this occasion 75 grams glucose in 450 c.c. of weak tea. The general condition of the patient was the same as at the time of the previous test. The results are shown in Table II and Chart II, Case II.

One sees that in this second test the alimentary hyperglycemia was delayed and prolonged. The greatest concentration occurred at the end of two hours while his normal value had not been reached at the end of six and a quarter hours.

The rate of urinary excretion decreased during the development of the hyperglycemia and was practically uninfluenced by the fluid intake. The rate of sugar excretion again fell rapidly with the development of the hyperglycemia and had not begun to increase by the end of the test.

If one were to judge this case by a consideration of the concentration of sugar in the urine it would seem that we had a patient who excreted urine containing about 0.5 per cent. glucose and that this was independent of the blood sugar up to the latter's concen-

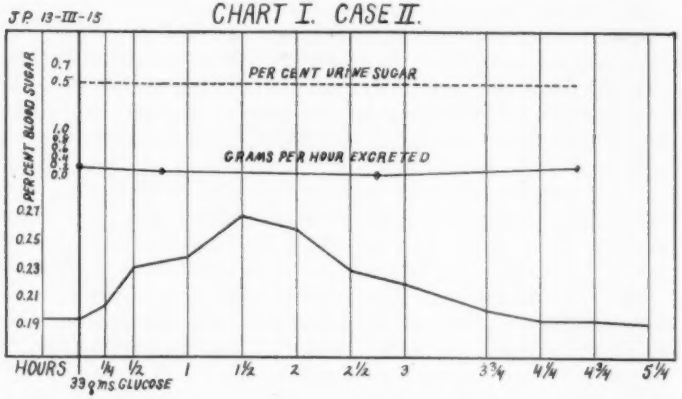
[21] C. V. Bailey: Proc. Soc. Exper. Biol. and Med., 1916, xiii, 153.

tration of about 0.26 per cent. At this point the kidneys became intolerant and more sugar appeared in the urine.

TABLE V.—CASE II.

J. E. P., December 13, 1915.

Time.		Blood.		Urine.					
A.M.		Hemoglobin. Units.	Sugar. Per cent.	c.c. per hour.	Sugar. Per cent.	Sugar. Grams per hour.	Specific gravity.	Chlorides, grams per hour.	Fluid intake. c.c.
9.25	....	67.5	0.196	42	0.52	0.220	1015	0.193	250
9.30		33 grams glucose.							
9.45	¼ hr.	64.0	0.208						
10.00	½ hr.	65.0	0.234						
10.30	1 hr.	65.5	0.240	36	0.51	0.186	1015	0.123	250
11.00	1½ hrs.	67.5	0.270						
11.30	2 hrs.	67.0	0.260						
12 M.	2½ hrs.	68.0	0.232						
12.30	3 hrs.	67.5	0.224	33	0.51	0.170	1016	0.142	
1.15	3¾ hrs.	67.5	0.204						
1.30									
1.45	4¼ hrs.	67.5	0.196						
2.15	4¾ hrs.	68.0	0.196	42	0.52	0.210	1013	0.190	
2.45	5¼ hrs.	67.5	0.192						



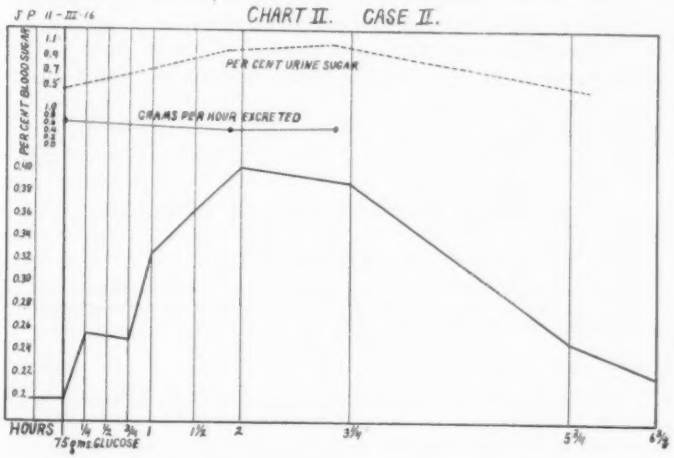
However, we see that the reverse is the case when we consider the actual excretory work done by the kidneys, the glucose being expressed in grams per hour. In Table I the kidneys excreted 0.22 gram of glucose per hour when the blood sugar was 0.196 per cent.; as the blood sugar increased the excretion of sugar decreased, so that when the blood contained 0.24 per cent. the sugar excretion had dropped to 0.17 gram per hour. The rate of excretion increased to 0.216 gram per hour when the blood sugar returned to the original

value, 0.196 per cent. In Table VI, Case II, Chart II, Case II, the same observations can be made.

TABLE VI.—CASE II.

J. E. P., March 11, 1916.

Time.		Blood.		Urine.				
A.M.		Hemoglobin. Units.	Sugar. Per cent.	c.c. per hour.	Specific gravity.	Sugar.		Fluid intake. c.c.
						Per cent.	Grams per hour.	
9.20	....	65.0	0.20	144	1015	0.5	0.72	
		75 grams						
9.30	....	glucose.	.....	...	....	...	....	450
9.45	½ hr.	65.0	0.258					
10.05	½ hr.	65.0	0.256					
10.20	1 hr.	64.0	0.252	52	1013	1.0	0.52	
10.35	1 hr.	64.0	0.329					
11.00	1½ hrs.	63.5	0.368	...	....	...	....	250
11.20								
11.30	2 hrs.	63.5	0.405					
12.45	3¼ hrs.	64.0	0.390	56	1015	1.1	0.61	500
1.30								
3.15	5½ hrs.	65.0	0.250					
4.15	6½ hrs.	65.0	0.220	?	1014	0.5	?	
7.35								



Summary. The case reported gave the subjective and objective symptoms of chronic parenchymatous nephritis. Nothing in the patient's history or in the physical finding would lead one to suspect a disorder of carbohydrate metabolism. He had a constant hyperglycemia, but no higher than is ordinarily found in chronic nephritis. The blood sugar curve following the ingestion of glucose was of the

type found in non-diabetic nephritis. Of special interest is the fact that glucose constantly appeared in his urine and that the rate of excretion was greatest when the blood sugar concentration was low. A hyperglycemia was accompanied by a decreased excretion of sugar.

CONCLUSIONS. Renal diabetes, or better "renal glycuresis,"[22] should be broadly considered as a condition of glycuresis not dependent upon a temporary increase of blood sugar in an individual free from symptoms of diabetes mellitus.

The condition can be recognized by morning synchronous blood and urine sugar tests, the specimens being collected before the patient has had anything to eat or drink.

At least two types can be recognized: (1) Cases with normal or subnormal blood sugar and glycuresis, which is greatly influenced by blood sugar changes; (2) cases with a constant glycuresis which varies with the rate of urinary excretion and is little influenced by blood sugar changes. The possibility of renal glycuresis being in some cases a congenital condition; the question whether or not the clinical course remains permanently free from symptoms of diabetes mellitus; the lack of reserve energy which such a condition produces, if severe; the direct effect upon the kidney of continued excretion of sugar are interesting points to be observed in this condition.

I wish to thank Professor Edward Quintard, director of the department of medicine, and Professor Victor C. Myers, director of the laboratory of pathological chemistry, for helping me in this work.

MULTIPLE ENDOTHELIOMA OF THE SKIN.

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CONCEPTION OF ENDOTHELIOMA AS AN ENTITY. Dermatological literature records many instances of single and multiple tumors which clinically were thought to be various types of nevi or sarcoma or syringocystadenoma, and which, after microscopic study, were identified as endothelioma by some and as epithelioma or carcinoma by others. Gottheil,[1] for example, published the report of a case of a pigmented tumor of the foot which clinically was considered to be a pigmented sarcoma or melanoma, but on section proved to be an

[22] Benedict, S. R., and Osterberg, E.: Jour. Biol. Chem., 1918, xxxiv, 258.

[1] Endothelioma of the Skin, Jour .Am. Med. Assn., January 12, 1907, xlviii, p. 93.

endothelioma. Juliusberg[2] reported a tumor of the abdomen, the histological structure of which induced him to classify the growth with the endothelioma group. His microscopic interpretation was severely criticized by a number of competent pathologists, such as Krompecher,[3] Ribbert,[4] Hoffmann,[5] Fick[6] and Friboes.[7] These authorities believed that with one or two rare exceptions all the so-called endotheliomas are in reality benign types of basal-cell epitheliomas or carcinomas. Fick somewhat vehemently asserted that the entire conception of endothelioma was an erroneous one, based on false interpretations of the histological pictures, and that an endothelioma never saw the light of day. His contention was that the so-called endothelial cells are actually epithelial cells, derived probably from the glandular structures of the skin. In a paper which he published under the title of "The Impracticability of 'Endothelioma' as a Working Hypothesis" (which I abstracted in the *Journal of Cutaneous Diseases* several years ago),[8] Fick not only criticizes all those writers who had the temerity to regard a growth as being an endothelioma, but severely arraigns those who permitted themselves to believe that such a conception is within the bounds of possibility.

In 1902 Borst[9] undertook the task of analyzing the microscopic findings of most of the tumors said to be of endothelial origin, and came to the conclusion that some of them undoubtedly deserved the title of endothelioma. In the following year his views were strongly opposed by Krompecher,[10] who contended that all of the so-called endotheliomas were epitheliomas or carcinomas, having their origin either from the basal-cell layer of the superficial epithelium of the follicles or of the glandular epithelium, and the cellular elements of which corresponded in every way with those of the basal cells. He therefore called them basal-cell epitheliomas, and his opinions, as before mentioned, were accepted by a large number of investigators. Zeit,[11] in 1906, published a very instructive article on the subject, in which he maintained that certain forms of sarcoma and carcinoma were in reality examples of endothelioma. Zeit's views are seldom

[2] Lymphangio-endothelioma Cutis Abdominis, Arch. f. Dermat. u. Syph., 1908, lxxxix, p. 77.

[3] Zur Histogenese und Morphologie der Mischgeschwülste, Ziegler's Beitr., 1908, xliv, p. 51. Ueber die Beziehungen zwischen Epithel. und Bindegewebe, Ziegler's Beitr., 1908, xliv, p. 131.

[4] Das Karzinom des Menschen, Bonn. 1911.

[5] Case Demonstration, Deutsch. med. Wchnschr., 1910, I, p. 2365.

[6] Ueber die Endotheliome der Haut, Monatsh. f. prakt. Dermat., 1909, xlviii, p. 199. Ueber die Unbrauchbarkeit der Arbeitshypothese "Endotheliome," Dermat. Wchnschr., 1912, liv, p. 488.

[7] Beitrag zur Klinik und Histopathologie der gutartigen Hautepitheliome, S. Karger, Berlin, 1912.

[8] Jour. Cutan. Dis., 1912, p. 444.

[9] Die Geschwülste, 1902.

[10] Das Basalzellenkrebs, Fischer, Jena, 1903.

[11] Endothelioma, Jour. Am. Med. Assn., 1906, xliv, p. 567.

if ever mentioned in the foreign literature, but they receive a well-earned recognition in Hazen's[12] book on *Skin Cancer*. Hazen classifies the endotheliomas under three heads: lymphangio-endothelioma, hemangio-endothelioma and perithelioma. With regard to the last, Hazen says: "The perithelial tumors originate from the endothelium lining the perivascular lymph spaces, and hence there is some discussion as to whether they should be called hemangio-endotheliomas or lymphangio-endotheliomas, according to some authors. On the other hand, Zeit emphatically says: 'The perithelial membrane must be differentiated from the perivascular lymph spaces of His, which he found surrounding the adventitia of arteries, veins and capillaries of the central nervous system. The perithelium is the outer lining of the adventitia of bloodvessels, outside of which is the perivascular lymph space.' Zeit further states that the true peritheliomata are the tumors arising from the perithelium and not from the lymph space, and hence should be called hemangio-endothelioma perivasculare. At any rate, up to the present time there is in the literature but one definite case report of a perithelioma of the skin, and that is a case reported by Brandeis and Pouget,[13] in which there were a number of metastases from a tumor of the adrenals." Hazen then devotes several paragraphs to Zeit's conception of the histological differences between endothelioma and carcinoma.

A compilation of 25 cases of tumors which had been designated as lymphangio-endotheliomas was made by Friboes in 1912. Of these, 3 examples were under his own observation, and his monograph includes a complete study of these as well as of nearly all other cases recorded in the literature. (The cases of Gottheil,[1] Allen[14] and Hartzell[15] are not included). Most of these growths were described as multiple tumors of the scalp and trunk. Many of them corresponded to the peculiar turban-like tumors of the scalp, described by Spiegler,[16] with which most readers are familiar, chiefly on account of the striking illustration of one of Spiegler's cases, seen in most of the older text-books. Of these 25 cases, 19 were in women and 6 in men. In 23, the tumors were multiple and single in 2. Their sites were: the hairy scalp only, in 10, the hairy scalp and the face in 1, the scalp and trunk in 9, the scalp, trunk and extremities in 5. The tumors appeared usually between the second and fourth decades. They varied in size from a pinhead to an orange; the small ones were usually rounded and sometimes lobulated; the larger ones were hemispherical, distinctly lobulated, with rounded, prominently bulging masses, the outline of the mass, as a whole, being

[12] Hazen: Skin Cancer, Mosby, St. Louis, 1916, p. 127.
[13] Ann. d. dermat. et de syph., 1910, 5th S., i, p. 506.
[14] Monatsh. f. prakt. Dermat., 1900, xxxi, p. 47.
[15] British Jour. Dermat., October, 1904. Diseases of the Skin, Philadelphia.
[16] Ueber Endotheliome der Haut, Arch. f. Dermat. u. Syph., 1899, l, p. 163.

aptly compared to that of a tomato. They were situated partly within and partly beneath the skin, resting on a broad sessile base. The masses were easily movable, but the skin covering them was usually quite adherent, especially over their central portions. Most of the tumors presented dilated bloodvessels in the skin which enveloped them. The closely set tumors were separated by deep grooves, within which the hair was still present, while their surfaces were entirely devoid of hair, excepting in the smallest tumors. The color of the more prominent masses was rose red, yellowish red, dark red or livid, with many tinctorial transitions. The skin covering the smaller tumors was usually normal in color. Small erosions of the surface of some of the larger tumors sometimes occurred as a result of the accumulation of dirt, sweat and sebaceous material, giving rise to irritation. Breaking down of the tumors occurred in 3 instances (Haslund,[17] de Beurmann[18] and Friboes[19]). Metatases took place in 2 (Ancell[20] and Haslund). Autopsies were performed in five of the patients (Ancell, Riehl,[21] de Beurmann, Friboes and Leeuwen).[22] In Ancell's patient there were severe visceral metastases, in the other four no signs of metastases were discoverable. Recurrences of the growth *in loco*, after extirpation, occurred only in Ancell's case.

Summing up his conclusions, based on a thorough analysis of these 25 cases, Friboes states his belief that with very few exceptions they represented examples of very slowly developing, peculiar types of benign epitheliomas.

In his recently published text-book Hartzell[23] summarizes the subject of cutaneous endothelioma in these words:

"The nature of the neoplasm is still a matter of some uncertainty. As already noted the earlier cases were regarded as a form of sarcoma, but this view is no longer entertained. In its prolonged and benign course and in its histopathology it is quite unlike any of the varieties of that neoplasm. Most recent authors agree with Spiegler in classifying it as an endothelioma. Quite recently, however, Dubreuilh and Auché, who have studied its histopathology with great care and detail, expressed the opinion that it is a variety of multiple benign epithelioma, having its origin in the epidermis and perhaps the hair follicles, and resembling much, in the character of the cells which compose it, rodent ulcer.

"According to Spiegler the tumor is composed of branching and

[17] Multiple Endotheliome der Kopfhaut, Arch. f. Dermat. u. Syph., 1906, 82.

[18] Cylindrome de la face et du cuir chevelu, Ann. d. dermat. et d. syph., 1911, p. 577.

[19] Loc. cit.

[20] Quoted by Friboes (loc. cit.).

[21] Endotheliom der Haut, Monatsh. f. prakt. Dermat., 1894, xix, p. 434.

[22] Multiple Epitheliome der Haut mit Mischgeschwülst der Parotis, Virchows Arch., 1912, ccvii, p. 330.

[23] Loc. cit.

intersecting cylindrical tracts of cells resembling small epithelial cells occupying the derma. About the margin of these tracts, which are surrounded by a fine fibrous capsule and contain numerous small round and oval masses of hyaline material, the cells are of the columnar type and are arranged radially, while those in the interior are round or polygonal."

Soft Nevi. Before taking up the description of the cases which form the subject of this paper, I should like to revert to certain anomalies or pathological changes in the skin which are of interest, both from the clinical and histological standpoint, in connection with cutaneous endothelial growths. The first of these are the soft nevi. Demieville,[24] in 1880, was the first to attract attention to the so-called nevus cells occurring in groups, strands and isolated areas within the corium. These were thought by him to be derived from the endothelial cells of the blood capillaries, and the nevi were looked upon as being endothelial tumors. Von Recklinghausen,[25] in 1882, stated his belief that the nevus cells had their origin in the endothelial cells lining the lymph spaces. His theory was that nevus cells, derived from the endothelial cells of some of the vessels, would develop in a certain area of the integument, through the growth of individual cellular elements which proliferated and were transformed into so-called nevus cells. Unna,[26] in 1893, opposed the view that these specialized cells were of endothelial origin and offered a number of reasons for considering them to be of epithelial origin. He based his opinions on the microscopic examination of a considerable number of soft nevi occurring in the newborn and stated (in his *Histopathology*, 1894) that the epithelial derivation of the nevus cells was demonstrable with much greater facility in preparations of nevi from the newborn as compared with those studied from the adult. Many subsequent writers, such as Delbanco, Kromayer, Gilchrist, Ravogli, Whitfield and Krompecher,[27] have since subscribed to Unna's views, so that by many it has become an accepted dictum that the derivation of nevus cells from the epithelial elements has been satisfactorily demonstrated in a number of instances, more especially in the soft nevi of the newborn, but also in isolated adult preparations.

Syringocystadenoma. The second type of lesion deserving mention in this connection is syringocystadenoma. Here, however, the interest lies chiefly in the clinical features which characterize this condition. Of the two cases of endothelioma which form the subject of this report, one presented a clinical picture which was almost identical with that of syringocystadenoma as it appears on the trunk. With regard to its histopathological features, an over-

[24] Quoted by Unna, Histopathologie, 1894.
[25] Quoted by Fick: Monatsh. f. prakt. Dermat., 1909, xlviii, p. 199.
[26] Histopathologie der Haut, 1894.
[27] Quoted by Fick: Monatsh. f. prakt. Dermat., 1909, xlviii, p. 205.

whelming majority of investigators have shown that the canals and cellular strands and the lining of the cysts are of epithelial origin, not endothelial. In some cases it has been successfully demonstrated that there is no breach of continuity between the lining of the cyst walls and the excretory ducts of the sweat glands. The epithelial derivation of these tumors is recognized by Darier and Jacquet, Unna, Jadassohn, Fordyce, White, Sutton, Hartzell, Heidingsfeld[28] and many others.

NEVO-XANTHO-ENDOTHELIOMA. Lastly, I must devote a few words to a type of new growth which McDonagh[29] aptly named nevo-xantho-endothelioma. In the second case of endothelioma, which will be described further on, I made the erroneous clinical diagnosis of urticaria pigmentosa or xanthelasmoidea, a diagnosis with which many of my colleagues concurred without hesitation. Microscopic examination demonstrated the fact that the tumors consisted of cells of endothelial origin. McDonagh described several cases which can be classed in this group, most of them having been diagnosed as urticaria pigmentosa, xanthelasmoidea, multiple angiomata, etc., until microscopic examination revealed them to be new growths of endothelial origin.

REPORT OF CASES.

CASE I (see Figs. 1 and 2).—*Endothelioma Simplex.* Abner W., male, aged thirty-two years, a native of this country, was unmarried and a clerk by occupation. He applied at the dermatological dispensary of Mt. Sinai Hospital for the removal of numerous "moles" on various parts of the body. He stated that these little growths first made their appearance in early childhood and had been few and widely scattered until about ten years ago, when his attention was attracted to several scores of new lesions on the chest and back. His account of the trouble was quite vague and unreliable, as he always had considered the blemishes as a trivial matter and paid very little attention to them. More recently, many comedones and acne papules and pustules had appeared on the chest, mingling with the older tumor-like growths in this locality.

History. The father died of endocarditis; the patient said that many "similar blemishes" had been present on his father's back and chest, but he did not know at what age they had appeared; as far as he knew they never gave his father cause for complaint. Two brothers of the patient had several "moles" on the chest and back, but whether or not they resembled his own, he was unable to say.

[28] Quoted by Hazen: Skin Cancer, p. 102.

[29] Nevo-xantho-endothelioma, British Jour. Dermat., 1912, xxiv, p. 85. Also, Biology and Treatment of Venereal Diseases and the Biology of Inflammation and its Relationship to Malignant Disease, London, 1915.

His mother and two sisters were free of cutaneous disorders or blemishes.

Physical Examination. The patient was well built and in good health. Physical examination was negative, save for disease of one ear, said to have resulted from a fall on the head in infancy, and causing deafness.

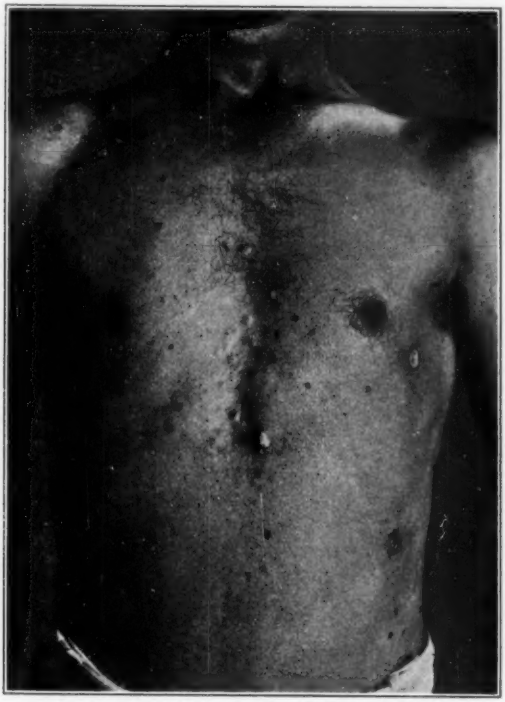

FIG. 1.—Case I. Multiple endothelial tumors of the skin. Comedones and acne over the sternum. The crusted lesions on the left side are sites of biopsies.

Description of Eruption. Between 125 and 150 papular lesions were scattered on various parts of the body. They were most abundant on the chest and back, more widely scattered on the arms, thighs and the neck. The face and scalp, forearms, legs, hands and feet were free.

The lesions consisted of well-formed papular elements, ranging in size from a pinhead to a lentil. They were soft and elastic. They varied in color: some were rose red, some brown, some salmon yellow, while a few, situated over the sternum, had the color of normal skin,

so that they were more readily felt than seen. Most of the little tumors were round or oval, projecting from a sixteenth to an eighth of an inch above the surrounding skin. The great majority of the tumors consisted of single well-defined and distinct papules; others, however, appeared to have formed as the result of the coalescence of two or even three individual growths, producing a lobulated or segmented structure. The skin covering the tumors was soft,

FIG. 2.—Case I. Side view of the same patient.

velvety and wrinkled in the larger and older lesions and smooth and somewhat stretched over the smaller and younger ones. There were several flat, pea-sized growths on the inner and upper surfaces of the thighs, rather firm to the touch as compared with the others, and bearing a striking resemblance to xanthomata. None of the growths had ever broken down or ulcerated.

At the lower portion of the sternum were many large comedones and acne papules and pustules. (The crusted lesions on the left side of the chest, seen in the photograph, are the sites of biopsies.)

Subjective symptoms were absent, the patient desiring removal of the blemishes for cosmetic reasons alone.[30]

CASE II (see Fig. 3).—*Nevo-xantho-endothelioma.* Abraham W., male, aged twenty-two months, born in this country of Russian Jewish parentage, applied for treatment in the dermatological department of the Vanderbilt Clinic, January 6, 1917. The child's family history and personal history were negative.

Physical examination revealed a healthy, strapping infant, presenting a well-marked macular and papular eruption on the trunk and extremities, most abundant on the abdomen.

Description of Eruption. The eruption consisted of many hundreds of lentil to pea-sized macules and papules, the latter predominating. The macules were rose red and bluish red in color, faintly convex, round and oval in outline; the papules were more pronounced in color, most of them being yellowish brown and salmon yellow in tint; they averaged about the size of a split pea and were most prominent on the abdomen, gradually giving place to flat papular and barely raised macular lesions on the chest and extremities; the back and the buttocks also were studded with well-defined papules. There were no urticarial wheals nor evidences of pruritus, although the mother stated that the eruption was preceded by a rash resembling mosquito bites. The disease first manifested itself when the infant was about a year old. No fresh lesions had recently appeared. The face, scalp, neck, hands and feet were free. There were no signs of dermographism. Pressure on the lesions with a piece of glass did not result in a lessening of their color to any appreciable extent.

The eruption was labelled urticaria pigmentosa or xanthelasmoidea. The child was again observed about six months later and the eruption had remained unaltered.

CLINICAL DIFFERENTIATION. The eruption in Case I closely simulated two cutaneous anomalies: ordinary soft, pigmented moles or nevi, and syringocystadenoma. Taking an individual lesion for a criterion of clinical diagnosis it would be impossible to differentiate it from an ordinary soft mole; but on considering the multiplicity of the tumors, their unusually widespread dissemination, the variations in color and surface markings, the lobulated formation of some of them, the problem of arriving at a clinical diagnosis remained unsettled. The resemblance to syringocystadenoma was less suggestive; still, that condition called for careful consideration: the history of the eruption, the distribution and size of the lesions, their insidious appearance, the absence of subjective sensations and various other factors, such as the occurrence in several members of the family, justified at least a serious consideration of the alter-

[30] The blemishes were removed by applications of trichloracetic acid. There has been no recurrence in a year.

native diagnosis. In syringocystadenoma, however, the little tumors are rarely if ever so deeply tinted (except when they occur in the negro, of which I have seen two examples); the tumors are not so sharply defined; their peripheries slope and the individual papules are frequently bordered by a narrow band of erythematous or pigmented skin; the endothelial tumors, on the other hand, were quite sharply demarcated, with abrupt peripheries; the elements of syringocystadenoma give the impression of being *in* the skin, while the endotheliomata in this patient readily impressed the observer as being *on* the skin.

With regard to the second patient, the infant, little more can be said except that the clinical diagnosis of urticaria pigmentosa was concurred in by a dozen competent dermatologists. Not until the microscope revealed the true state of affairs did anyone entertain the slightest suspicion that the eruption was composed of formations resulting from endothelial cellular proliferation.

As stated, McDonagh christened this dermatosis nevo-xantho-endothelioma. To those who are uninitiated in the complexities and niceties (?) of dermatological nomenclature the prefix, nevo-xantho may be a source of confusion. A nevus is a blemish which may be present at birth, may appear early in infancy and sometimes even in late adult life. "Xantho" refers, of course, to the yellow tint of the lesions. Now it so happens that urticaria pigmentosa is also known under the name of xanthelasmoidea, on account of the close similarity, clinically, to the little tumors of xanthoma. Some eruptions of urticaria pigmentosa simulate xanthomata to such an extent that only a microscopic examination can tell them apart. McDonagh calls attention to the erroneous diagnosis of urticaria pigmentosa or xanthelasmoidea applied to eruptions which proved (as in Case II), on microscopic examination, to be endotheliomata, appearing at birth or early in infancy. Hence the name, nevo-xantho-endothelioma.

In this connection attention should be called to the fact that the lesions in Case I also would by many pathologists be regarded in the light of nevi of endothelial origin. From the pathologist's point of view a nevus may make its appearance at any period in life; the pathologist's conception of the term embraces a far more comprehensive group of cutaneous anomalies than does that of the clinician; for example, ichthyosis, xeroderma pigmentosum, syringocystadenoma, benign cystic epithelioma, lymphangioma circumscriptum and several other morbid changes in the skin are by many considered to belong in the nevus group. This question, as already intimated, is still undecided. The whole subject is, I think, very interestingly discussed by McDonagh, in his chapter on "The Role Played by the Endothelial Cell in Inflammation and its Probable Relationship to Sarcoma." Most dermatologists will find this to be a rather refreshing bit of reading, and certainly well worth the while.

HISTOPATHOLOGY (see Figs. 3, 4, 5, 6, 7, 8, 9). Three tumors of different sizes and seemingly various ages were removed from Case I and one papule from Case II for purposes of microscopic study. These were sectioned and stained with hematoxylin-eosin, van Gieson, polychrome methylene blue, Unna-Pappenheim, acid-orcein and Weigert's elastic-tissue stains.

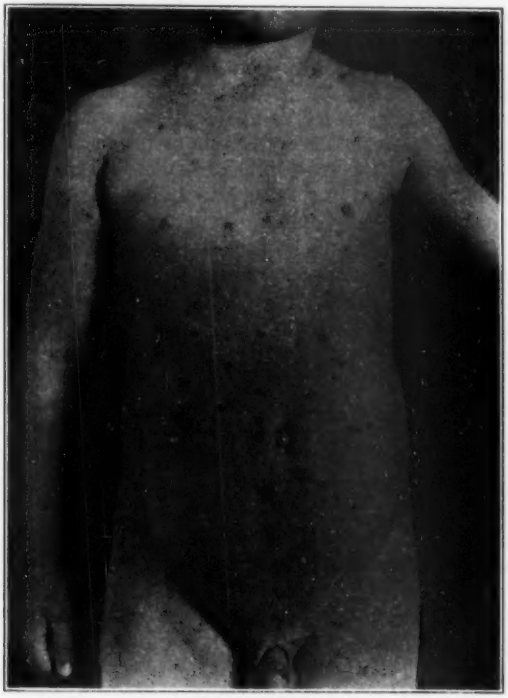

FIG. 3.—Case II. Endothelioma cutis. The eruption closely resembles urticaria pigmentosa.

The only noteworthy difference between the microscopic structures of the young and older lesions consisted in a correspondingly lesser or greater amount of cellular infiltration in the corium and in unimportant secondary changes in the epidermis, due to pressure exerted upon it by the underlying infiltrate. When the subepidermal infiltrate was sparse the epidermal layer was practically unaltered; when the infiltrate was abundant the covering epithelium was flattened and compressed. The sections here described were cut from a young lesion, and from another, apparently fully developed old lesion, taken from Case I, and from a fully developed pea-sized papule, taken from Case II.

FIG. 4.—Case I. Endothelioma, early lesion showing derivation of cells.

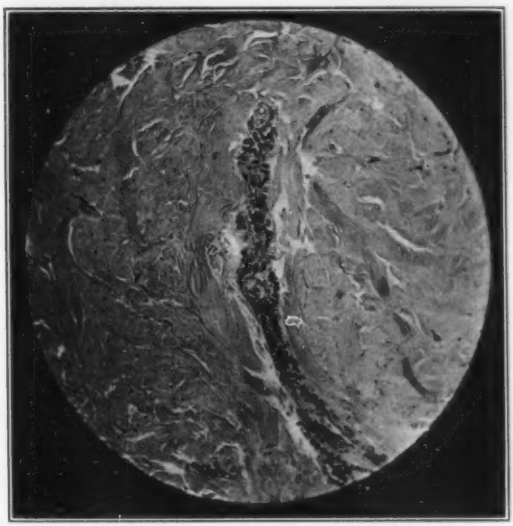

FIG. 5.—Case I. Endothelioma, early lesion showing derivation of cells.

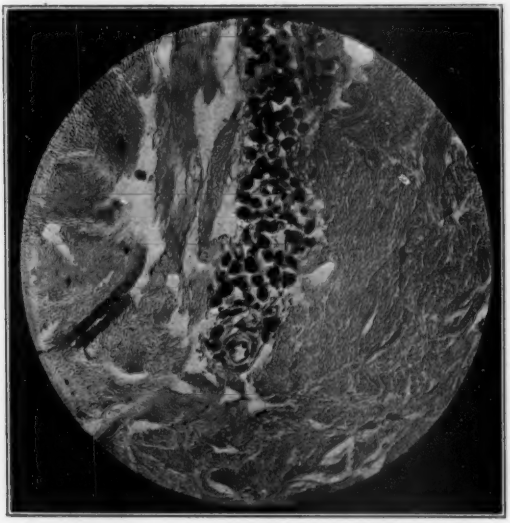

FIG. 6.—Case I. Endothelioma, early lesion showing derivation and type of cells.

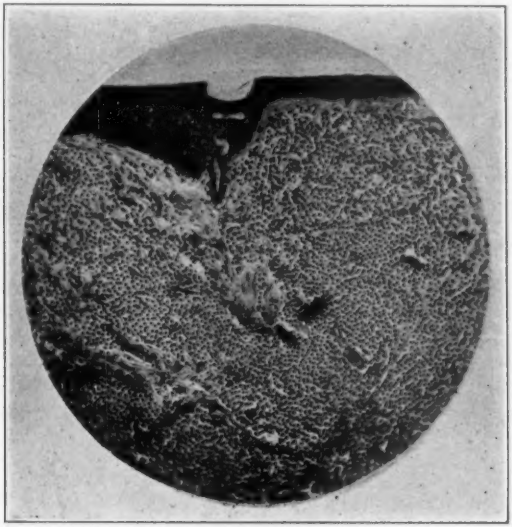

FIG. 7.—Case I. Endothelioma, late lesion showing widespread infiltration.

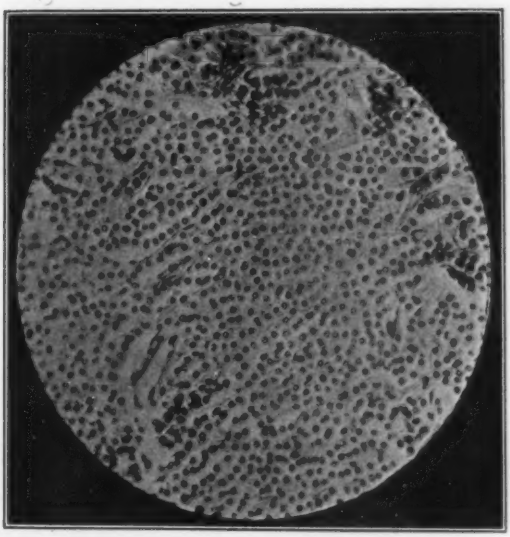

FIG. 8.—Case I. Endothelioma, late lesion showing type of cell.

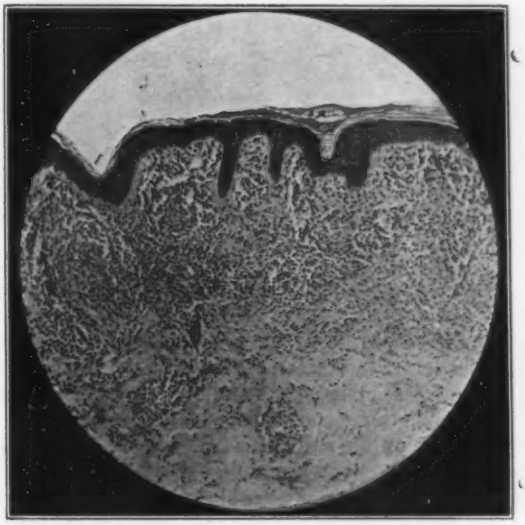

FIG. 9.—Case II. Endothelioma. The histopathology is almost identical with that of Case I.

Strikingly different as these three lesions appeared to the clinical eye they nevertheless presented practically identical pathological alterations under the microscope.

In the young growth the epidermis is but little altered; there is a moderate amount of hyperkeratosis and slight intercellular edema; in some places the basal layer presents a decided increase in pigment. In the corium there are irregularly disposed collections of cells, grouped mostly about blood and lymph vessels and filling the lymph channels and spaces. There is a moderate increase in the vascular supply, most pronounced in the upper half of the cutis.

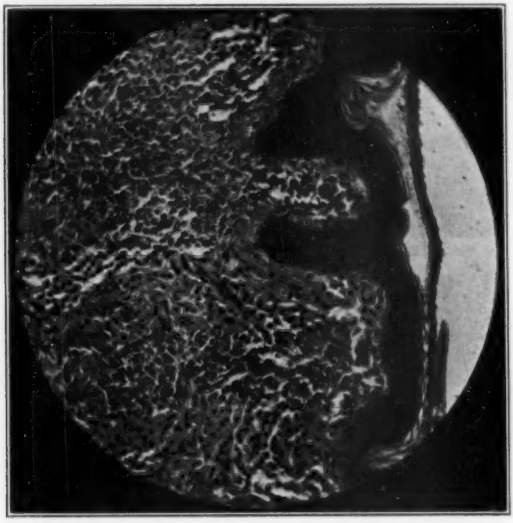

FIG. 10.—Case II. Endothelioma. High magnification of section of Fig. 9.

The connective tissue exhibits a mild grade of edema. Isolated cells and small groups of cells, morphologically identical with those composing the larger infiltrates, are scattered throughout the cutis, lying in the interfascicular spaces and in narrow lymph channels or clefts. The elastic tissue is diminished and fragmented.

In the older lesion the epidermis is decidedly thinned; the portion overlying the large area of subepidermal infiltration shows a complete absence of papillæ, the basal membrane forming a perfectly straight line. These changes in the epidermis are evidently due to pressure exerted by the underlying mass of infiltrating cells.

The upper two-thirds of the corium present a uniform, dense cellular infiltration. This mass of cells is roughly semicircular in

outline, the base of the semicircle opposite the basal layer of the epidermis, the peripheral segment rather sharply outlined against the adjacent, relatively cell-free and unaffected connective tissue of the deeper cutis. On either side of this infiltrate (on tangential section) the epidermis, relieved of pressure from below, resumes its normal appearance, maintaining the integrity of its papillæ. The dense cellular infiltrate embedded in the corium gives the impression of having displaced the connective tissue in the area occupied by it, an appearance intensified by the very sparse amount of connective tissue lying, in the form of fine fibrils and narrow strands, within the bounds of the cell mass. The upper boundary of the infiltrate is in some regions separated from the epidermis by a narrow band of compressed connective tissue; in other places the cells mingle with the lowermost layers of the epidermis, so that the sharp line of demarcation between epithelium and cellular infiltrate is lost.

This infiltrate is composed of closely massed cells of remarkably uniform shape and size. These cells possess a sharply defined, well-rounded, prominent nucleus and a distinctly outlined, round or oval, in some cases also polygonal cell body. The integrity of the protoplasmic body of the individual cells is maintained even where they are densely packed, so that a nice mosaic-like effect obtains. The morphological and tinctorial characteristics of these cells identify them as endothelial cells.

Although on superficial examination the disposition of the cell masses seems to bear no intimate relation to the structures lying within the confines of the infiltrate, closer inspection reveals the fact that they are grouped chiefly and most abundantly about the blood and lymph vessels. In some places the cells are ranged in vertical strands, separated by fine fibrils of connective tissue. In general these strands are disposed in a roughly radial fashion, like the outstretched fingers of the hand, the proximal ends lying in the papillary, the distal ends in the reticular portion of the cutis. There is a moderate increase in the vascular supply and a more pronounced increase in the lymphatic supply of the corium.

Under high power it is seen that the endothelial cells composing the infiltrate not only surround the blood and lymph vessels, but also occupy their lumina, in some places completely filling them, as well as the lymph channels, throughout the upper portion of the cutis.

The walls of the bloodvessels are not thickened; in fact, they appear to be unaltered save the proliferation of the intimal layer. The connective tissue of the corium, both within the infiltrating mass as also at its periphery, appears to be normal, aside from a moderate grade of edema. Evidences of hyaline degeneration are absent. The sebaceous and coil glands, of which the sections contain a few, are normal in appearance. The elastic tissue is

diminished in amount and fragmented throughout the entire cutis.

COMMENT. The outstanding feature in the histopathological structure of these little tumors is the cellular infiltrate, composed of endothelial cells, derived, in all probability, from the lining membranes of the blood and the lymph vessels in the corium.

The origin of these cells is the subject of much controversy in dermatopathological literature. To go into detailed discussion of the problem would be superfluous in this paper, for the readily accessible article on "Endotheliomata" by Zeit, the excellent monograph on *Skin Cancer* by Hazen and McDonagh's chapter on the "Endothelial Cell" deal fully with various phases of the subject and need not be transcribed here.

There can be no question that the histological picture herein described bears some points of similarity to certain types of carcinoma (rodent ulcer), sarcoma and so-called cylindroma, although when sections of these various tumor forms are studied side by side certain well-marked differences become immediately obvious.

Zeit points out the following differential histological features in carcinoma, sarcoma and endothelioma, incidentally emphasizing the character and disposition of the cells composing the infiltrate in the last-mentioned form of new growth:

1. "The tumor cells in endothelioma are intimately connected with the stroma and cannot be brushed out of the stroma, as in the case of carcinoma, in which the epithelial cells may also retract from the stroma and show spaces.

2. "Endothelial cells produce intracellular cement substance and are closely packed together, whereas the epithelial cells in carcinoma have no intercellular substance and form no compact layers.

3. "In endothelioma delicate fibrillar processes extend from the walls of the alveoli into the proliferated cell masses. They are absent in carcinoma.

4. "In endothelioma the cell masses consist of a dense mosaic of many layers of cells, with small, sharply outlined nuclei, surrounded by a broad envelope of clear, glassy perinuclear protoplasm. Carcinoma cells have large vesicular nuclei, with a moderate amount of perinuclear protoplasm, more or less granular.

5. "In endothelial tumors the cells are arranged in the form of cellular cords and cylinders (round masses in carcinoma) and may separate out hyaline material (cylindroma) or form lumina-like masses (sieve-like) in the cellular cords, due to secretory processes of endothelial cells.

6. "To distinguish the endothelial tumors from sarcomata it is to be remembered that the former have an organoid and the latter a histoid structure. According to this definition, every large-cell sarcoma with a well-developed stroma which was formerly called alveolar sarcoma would be called an endothelioma."

CONCLUSIONS. The type of endothelial new growth herein described is probably very rare, its literature being very scant. Most of the cases heretofore described were the so-called "turban tumors" of the scalp, first published by Ancell and later by Spiegler.

Clinically, tumors of endothelial origin may be indistinguishable from the efflorescences of urticaria pigmentosa, xanthoma, soft moles, syringocystadenoma, multiple benign cystic epithelioma and perhaps other dermatoses. The inference that the study of sections from cases of this kind would occasionally reveal new growths of endothelial origin seems justifiable.

The writer is indebted to Professor Fordyce for permission to publish the account of Case II from the dermatological department of the Vanderbilt Clinic, and to Assistant Professor MacKee for his kindness in supplying the photomicrographs.

CLINICAL RESULTS IN TWO HUNDRED TRANSFUSIONS OF CITRATED BLOOD

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INTRODUCTION. A little more than four years have elapsed since I first suggested the application of a minute dose of sodium citrate for use in blood transfusion. It seems to be the fate of every new suggestion in medicine that it encounters a great deal of skepticism. The citrate method was no exception to the rule. Experiments on animals[1] and a large series of cases in the human being (22 cases[2]) had proved the efficiency and harmlessness of this method beyond doubt. Yet most of the clinics in this country still continued to use the older and much more complicated methods (syringe-cannula method, paraffinized glass cylinders, etc.).

The skepticism, however, has vanished considerably in the last two years. It is safe to say that the vast majority of transfusions done in this country at the present time are citrate transfusions. The simplicity of the method, its safety and the efficiency were bound to appeal to the medical profession.

The Mayo Clinic was one of the first clinics to try this new method on a large scale. Their results are illustrated in the following note of

[1] Lewisohn: A New and Greatly Simplified Method of Blood Transfusion, Med. Record, 1915, lxxxvii, p. 141.

[2] Lewisohn: Citrate Method of Blood Transfusion, Surg., Gynec. and Obst., 1915, xxi, p. 37.

Dr. Pemberton[3]: "For the past two years we have been using the citrate method, as recommended by Dr. Lewisohn, almost to the exclusion of others, and it has proved eminently satisfactory. During this time we have employed it in between 900 and 1000 cases, and in no instance where chemically pure citrate has been used has there been any untoward result attributable to the method. The simplicity and sureness of the technic, the safety of its employment and the proved therapeutic value of the citrated blood should recommend the method for a more general adoption."

A commission, consisting of surgeons and serologists, now in service in France, has recently investigated the different methods and has recommended the method of citrated blood as the method of choice, because it is the most practical "under war conditions." Their conclusions are the following: "Of the many available methods the citrate method has been adopted, because:

(*a*) It is the simplest with respect to technic.

(*b*) It is the simplest with respect to equipment.

(*c*) It has given uniformly excellent results in a large number of cases and the presence of the citrate has resulted in no practical disadvantage.

(*d*) It is less of an operation to both donor and recipient, for it seldom necessitates an incision over the vein.

(*e*) It is virtually a medical procedure, thereby saving the surgical personnel for major surgical work in times of stress."[4]

HISTORY. The citrate method of blood transfusion, though only a few years old, has already a history of its own. It seems to be the trend of the human mind to work out new methods along complicated lines first and simplify them later. Ideas for possible improvements ripen very often in the minds of different investigators at about the same time. It was natural that the very cumbersome technic of the older methods of blood transfusion should stimulate research workers to simplify the technic; and it was further very natural that the idea of the use of anticoagulants should suggest itself as a very obvious way toward such simplification. As far back as 1908 this problem was approached by Lespinasse. In a discussion of Abelmann's paper on the technic of direct transfusion of blood, Lespinasse[5] said: "In 1908 and 1909 I convassed the problem (anticoagulants) thoroughly and found that peptone and hirudin are absolutely toxic and that sodium citrate in moderate amounts is quite toxic. In smaller amount it is not so toxic, but it is toxic. In hemorrhagic diseases any method that includes a noncoagulating element in the transfused blood is absolutely contraindicated."

[3] Janeway: Blood Transfusion, Course of Instruction on War Surgery, Cornell University Medical School, 1918.

[4] A Report upon Transfusion of Blood for the Recently Injured in the U. S. Army, May, 1918.

[5] Chicago Med. Rec., 1915, xxxvii, p. 589.

I have never claimed any priority for the idea of using anticoagulants in blood transfusion. For instance, sodium phosphate and sodium oxalate were tried as anticoagulants in blood transfusion in the last century, though without success, by Braxton Hicks[6] and Wright.[7]

However, it seems that it was my good fortune to show[1] that by using a minute dose of sodium citrate this anticoagulant could be used even for large blood transfusions without causing any toxic effects in the recipient. These experiments, furthermore, determined for the first time the maximal dose of sodium citrate for the human being (5 grams).

At exactly the same time (January, 1915), Agote,[8] of Buenos Ayres, published an article on the same subject. It is a peculiar coincidence that both these investigations went on at the same time and were published contemporaneously.

Agote's dose (0.25 per cent.) is perfectly safe and amply sufficient to prevent coagulation. His investigations, however, were less thorough, as he did not study the question of maximal dosage. Furthermore, his stock solution (25 per cent.) is too strong. Thus, during the collection of the initial 100 to 200 c.c. of blood the very strong concentration of his stock solution is apt to destroy vital elements of the blood.

A few months previous to our publications Hustin,[9] of Brussels, had published a report on the same subject. However, as Hédon has shown, his method and the results of his experiments have really not answered the problem in question: "He mixed in equal parts blood with an isotonic glucose-salt solution, containing a certain proportion of sodium citrate, and injected this mixture in small quantities. Thus, Hustin's method of transfusion is really an infusion of a strongly diluted blood mixed with citrate of soda and glucose." (Hédon.[10])

The technic of citrate transfusion consists of two distinct steps: The first, that of properly preventing coagulation of the blood as it is collected from the donor, is the step of major importance. The second, that of its introduction into the blood stream of the recipient regardless of the type of apparatus used, is of distinctly minor importance.

The conclusiveness of the original experiments which were the basis of the citrate method (minimal and maximal dosage, etc.), made it apparent from the start that no important changes would

[6] Cases of Transfusion, with Some Remarks on a New Method of Performing the Operation, Guy's Hosp. Rep., 1869, xiv, p. 1.

[7] A New Method of Blood Transfusion, British Med. Jour., 1891, ii, p. 1203.

[8] Nuevre procedimento para la transfusion del sangre, Anales del. Inst. mod. de Clin. Med., 1915.

[9] Principe d'une nouvelle méthode de transfusion muqueuse, Jour. Méd. de Bruxelles, 1914, xii, p. 436.

[10] Note complémentaire sur la transfusion du sang citraté, Presse méd., 1918, xxvi, p. 57.

be made by further investigations in this direction. On the other hand, it was to be expected that many new suggestions would be made in reference to the apparatus. The apparatus, as originally suggested by the author, seems to have the advantage of utmost simplicity. An ordinary glass jar and a salvarsan flask represent the essentials of this outfit. Pemberton,[11] Heyd,[12] Williams,[13] Graves,[14] Garbat,[15] McKay,[16] and many others have published their results and expressed their perfect satisfaction with the author's original technic. Later modifications by different authors (Singleton,[17] Stansfeld,[18] Mumey,[19] Janeway,[20] Zingher,[21] Abelmann,[22] Jeanbrau,[23] etc.) have not acquired general popularity, as they are not more efficient than the simple outfit in its original form.

Special apparatus has the disadvantage of not being at hand when the emergency for blood transfusion may arise, whereas a graduated glass jar and a glass funnel with a piece of rubber tubing are always at hand, even in the smallest hospital, or can be procured from any drug store.

There can be no objection to individual surgeons using special outfits according to their preference. It is, however, not advisable to try to combine the application of sodium citrate with the older methods, either syringe method (Zingher,[24] Abelmann[25]) or Kimpton-Brown glass cylinders (Jeanbrau[26]). The disadvantage of the Kimpton-Brown tubes is that the method requires exposure of the vein of the donor. To use these tubes in combination with the citrate method, as Jeanbrau has suggested, complicates the citrate method unnecessarily and would tend to make the method less popular.

Jeanbrau's work has helped a great deal toward popularizing the citrate method in France. Hédon[27] had worked out the experi-

[11] Loc. cit.

[12] Blood Transfusion, with Special Reference to the Citrate Method (Lewisohn), New York Med. Jour., 1917, cvi, p. 57.

[13] Lewisohn: Citrate Method of Blood Transfusion, etc., U. S. Naval Med. Bull., 1916, x, p. 503.

[14] Blood Transfusion in Anemiæ, Texas State Jour. Med., 1917, xiii, p. 137.

[15] Intravenous Injections of Sodium Citrate with Reference to Transfusion, Jour. Am. Med. Assn., 1916, lxvi, p. 1543.

[16] McKay-Lewisohn Method of Blood Transfusion, Med. Jour. of Australia, 1916, i, p. 217.

[17] A Reliable Method of Blood Transfusion, Southern Med. Jour., 1916, ix, p. 439.

[18] An Apparatus for the Transfusion of Blood by the Citrate Method, Lancet, 1918, cxliv, p. 334.

[19] Apparatus for Transfusion of Blood by the Sodium Citrate Method, Jour. Arkansas Med. Soc., 1917, xiii, p. 158.

[20] Loc. cit.

[21] A Simple Syringe Method for Transfusion of Blood in Children, New York Med. Rec., 1915, lxxxvii, p. 440.

[22] Blood Transfusion Simplified by the Use of Citrate Ointment, Surg., Gynec. and Obst., 1918, xxvii, p. 88.

[23] Technique simple du transfusion du sang stabilisé par le citrate de soude, Presse méd., 1918, xxvi, p. 58.

[24] Loc. cit. [25] Loc. cit. [26] Loc. cit. [27] Loc. cit.

mental basis of the method, at the suggestion of Jeanbrau, and without knowing anything of the work done in this hemisphere. Both authors published their results in 1917. It is a great satisfaction that Hédon's conclusions coincide in practically every detail as to minimal and maximal dose, etc., with the author's results. Hédon and Jeanbrau have acknowledged Agote's and the author's priority claims. Jeanbrau's pupils (Murard,[28] etc.) have called the citrate method in a series of publications "la méthode de Jeanbrau." For reasons above given it seems advisable to adhere to the original name suggested by the author, "citrate method." Otherwise, we would in a very short time have the same method called by a dozen different names according to different apparatus used in its execution. As stated above, the important principle is the application of sodium citrate; modifications of apparatus are of minor importance.

INDICATIONS FOR TRANSFUSION. The following review is based upon the material of 200 transfusions (150 cases) which I had occasion to collect during the past three years. Such material is moderate in size compared to large series collected in the present war. However, it has the advantage of showing the usefulness of blood transfusion in a great variety of diseases, whereas the application of transfusion in the theater of war is limited to hemorrhage, shock and sepsis. The vast majority of the transfusions were performed at Mount Sinai Hospital. Some were obtained in private practice and others in different hospitals in New York (Roosevelt, Presbyterian, Beth Israel, Lebanon, St. Luke's, Lenox Hill Hospitals) in the early part of 1915, where I was asked to demonstrate this new method. I beg to thank the attending physicians and surgeons who had charge of the cases for their kind permission to use the records.

It is well known to what extent the technic of blood transfusion has been revolutionized during the past ten years. Crile's direct vessel anastomosis and Landsteiner's work on hemolysis and agglutination are monumental mark-stones in the development of the technic of blood transfusion.

The indications for blood transfusion, however, have changed very little during the last fifty years. A perusal of the literature (Belina-Swiontkowski,[29] Gesellius,[30] Jennings,[31] etc.) shows that in the middle of the last century transfusion was used in a great variety of diseases (hemorrhage, leukemia, hemophilia, CO poisoning, tuberculosis, eclampsia, etc.). To be sure, the usefulnes of blood transfusion has been materially widened since the invention of safe methods for its performance. Very few new indications for blood transfusion, however, have been added in this era of technical perfection of blood transfusion.

[28] La transfusion du sang veineux citraté par le procédé de Jeanbrau, Lyon Chir. 1918, xv, p. 147.

[29] Transfusion des Blutes, Heidelberg, 1869. [30] Ibid., Petersburg, 1873.

[31] Transfusion, London, 1883.

It is not the object of this paper to discuss blood transfusion in all its different aspects. Ottenberg and Libman's paper[32] and Bernheim's[33] book published recently have covered the subject so extensively that a thorough presentation of the whole subject at the present time would simply mean a repetition. I therefore prefer to review some points of interest which I had occasion to observe in collecting the 200 cases of transfusion of citrated blood and to dwell on such points as to value and efficiency of the citrate method which are still subject to discussion.

TABLE I.—RESULTS OF TRANSFUSION OF CITRATED BLOOD.

Disease.	Number of cases.	Number of transfusions.	Cured.	Improved.	Not improved.	Unknown.	Died.
1. Hemorrhage:							
(*a*) Hemophilia and allied conditions	14	15	11	..	..	..	3
(*b*) Purpura	16	20	4	5	..	2	5
(*c*) Gastro-intestinal hemorrhage	11	20	2	1	..	..	8
(*d*) Cholemia	5	11	..	..	..	..	5
(*e*) Postoperative hemorrhage	13	16	6	..	..	..	7
(*f*) Hemorrhage from female genital organs	2	2	..	..	..	..	2
(*g*) Traumatic hemorrhage	2	3	1	..	..	..	1
2. Diseases of the blood:							
(*a*) Pernicious anemia and leukemia	24	39	..	7	4	..	13
(*b*) Primary and secondary anemia	4	7	3	1			
3. Preoperative and postoperative transfusions	35	39	12	..	..	..	23
4. Sepsis	5	7	..	..	..	..	5
5. Incurable conditions (transfusions performed at request of family)	12	12	..	..	..	..	12
6. General debility	6	8	..	1	..	1	4
7. Acute poisoning	1	1	1				
Totals	150	200	40	15	4	3	88

In checking up the final results, such cases as were liable to die a short time after leaving the hospital, on account of the underlying disease (inoperable carcinomata, etc.), were put down as fatal results. Many of these cases leave the hospital temporarily strengthened on account of the transfusion. If they had been put down as "improved," as has been done in many other transfusion statistics, the death rate would have been lowered considerably. Furthermore, we have tried to follow up the final results in our cases. Thus a considerable number of cases which appeared to be cured or conconsiderably improved upon discharge, but died subsequently at home on account of a recurrence of their original disease, were put down as fatal results.

[32] Blood Transfusion, Am. Jour. Med. Sc., 1915, cl, p. 36.
[33] Blood Transfusion, Hemorrhage and the Anemias, 1917.

1. Hemorrhage.

The prime indication for blood transfusion will always be the restitution of blood lost in a profuse hemorrhage. The great therapeutic usefulness of transfusion in hemorrhage is, of course, not limited to hemorrhages caused by traumatic injuries to large vessels, but comprises just as well the hemorrhages occurring in typhoid fever, ectopic pregnancy, ulcer of the stomach, etc., and in hemorrhagic diseases (hemophilia, melena, etc.).

(*a*) *Hemophilia and Allied Conditions* (14 *Cases*, 15 *Transfusions;* 11 *Cures*, 3 *Deaths*).

The indication for transfusion in these cases was very profuse hemorrhage, seriously endangering the life of the patient. Nine of the patients were newborn babies, suffering from hemophilia neonatorum. They were all extremely exsanguinated and would have died in a few hours without a transfusion. A single transfusion saved six of these babies. Methods of procedure and the wonderful permanent cures obtained in these newborn infants have been discussed in a previous paper.[34]

Among the remaining 5 cases, 3 concerned children (two and one-half, three and eight years of age, respectively). The father of one child was a bleeder, the others did not come from bleeder families, yet they bled so profusely from small wounds, which ordinarily should have stopped bleeding spontaneously, that they were evidently hemophiliacs. Very little is known at the present time about the true status of this disease, and our diagnosis is mostly based upon the clinical symptoms of protracted bleeding from small wounds. In every one of these cases thromboplastin and horse serum had been tried, before transfusion had been resorted to. Horse serum, thromboplastin, coagulen, etc., are not nearly as effective as transfusion of blood. Though exact figures are not at hand, they seem to be effective, according to the personal experience of the author and reports in the literature, in about 30 per cent. of hemophiliac bleeding. They ought to be tried in every case. However, if they are not effective blood transfusion ought to be immediately resorted to without loss of valuable time.

In 2 of these cases the hemorrhage stopped immediately after one transfusion and the other required four transfusions before the curative effect was obtained. In the emergency of the first transfusion, while the patient is extremely exsanguinated and no available donor at hand, members of the family (after proper tests) are usually used as donors. If the first transfusion has not the desired

[34] Lewisohn: Blood Transfusion (Citrate Method) in Hemophilia Neonatorum, Am. Jour. Obst., 1918, lxxvii, p. 933.

effect, professional donors ought to be taken. It is a well-known fact, no matter what the primary disease may be, that if the first transfusion is not effective a second transfusion may stop the hemorrhage, if a different donor is obtained. The reason for this interesting and important observation is not known. However, its actual correctness has been noticed in many cases by different observers. Yet this fact, of vital importance as it is, is often overlooked, thus possibly causing death, where a perfect cure might have been obtained. Transfusion of blood, simple as it may seem, if we look at it from the purely technical point of view, requires thorough knowledge and strict observance of many fine points in order to obtain really good clinical results.

One of the few cases in this series of 200 blood transfusions, in which transfusion had to be resorted to without previous test for hemolysis and agglutination, was a boy, aged eleven years, who was admitted to Beth Israel Hospital with a large hematoma of the scalp following a slight injury. His maternal grandfather had died at the age of thirty-five from some uncontrollable hemorrhage. The boy had noticed the swelling four days before his admission to the hospital. As no facts about his bleeding tendency were known when the boy was admitted, and as the boy showed a marked protrusion and edema of the right eye (pressure from retrobulbar hematoma), an immediate incision about one and a half inches long was made through the skin above the swelling and a large collection of sanguinolent fluid drained off. No outward signs of bleeding followed. However, when I reached the hospital the next morning the boy was practically pulseless, as white as a sheet, showed extreme air-hunger, and was evidently in a dying condition. Luckily his father was standing at his bedside. Without any tests, 350 c.c. of blood were taken from the father and inside of fifteen minutes, after I reached the hospital, the boy had received this quantity of blood, which ensured his perfect recovery. In such a case minutes count, and if we had not used great speed the boy might have died before the blood was introduced into his veins.

The last case of this series, a man, aged thirty-two years, offered some points of interest as to his family history and as to the change of coagulation time following citrate transfusion. He told us that he had lost three brothers and six cousins (children of his mother's two sisters) following a ritual circumcision. Such a mortality is appalling. All these deaths occurred twenty to thirty years ago. Each one of these lives could probably have been saved by a single transfusion. I relate these facts here to point out the importance of transfusion of blood. Many physicians, even at the present time, consider blood transfusion as a somewhat spectacular and rather useless procedure. Here were nine lives wasted because the accidents occurred many years ago, before transfusion had been properly developed.

The coagulation time of this patient's blood before the transfusion was two and a half hours; twenty-four hours after the citrate transfusion it was only fifteen minutes. Tests taken three days later showed that it had come down to normal (five and a half minutes). If tests had been taken two weeks later they probably would have shown that the coagulation time had gone back to its previous state. As explained in a previous paper on this subject,[35] the shortening of the coagulation time is only temporary; it usually returns to its pre-transfusion stage in twenty-four to forty-eight hours.

(*b*) *Purpura Hemorrhagica* (16 *Cases*, 20 *Transfusions;* 4 *Cures*, 5 *Improved*, 2 *Results Unknown*, 5 *Deaths*).

We have in the previous chapter (hemophilia) confined ourselves to the discussion of one clinical symptom (hemorrhage) and its treatment by transfusion of blood. In the same way the discussion of purpura hemorrhagica must be limited to the investigation of results obtained by transfusion following profuse hemorrhages. A presentation of the pathological changes and clinical symptoms in purpura hemorrhagica would go far beyond the scope of this paper.

Blood transfusion in purpura is not nearly as effective as in hemophilia. It seems that some cases of hemophilia can be permanently cured, especially if done in infancy, by a single transfusion. The introduction of normal blood seems to repair the defect in the thrombus-forming mechanism and may thus result in a permanent cure. Results obtained in transfusion of purpuric patients are very unsatisfactory. In the majority of cases transfusion does not seem to influence the progress of the disease materially, though temporary benefit can be obtained. Thus cures in chronic purpura cannot be considered as permanent, though some of the patients were apparently in perfect health two years after the transfusions. Remissions of long intervals are frequently observed in purpura.

The predominant symptoms in five cases were very profuse menstrual bleeding, lasting for several weeks and so profuse that it very seriously endangered the life of the patient. The clinical significance of these menstrual flows, generally occurring in young girls between the ages of eighteen and twenty-four years, is very often overlooked by the general practitioner or gynecologist who tries to cure these cases by local treatment. Even hysterectomies have been performed to stop these hemorrhages.

Two of these girls had, in addition to the uterine bleeding, hemorrhages from nose, throat and gums, and their skin was scattered with

[35] Lewisohn: Importance of Proper Dosage of Sodium Citrate in Blood Transfusion, Ann. Surg., 1916, lxiv, p. 618.

ecchymotic spots. One of them was perfectly well two years later, the other died very soon after the transfusion. In the three other cases the bleeding stopped temporarily; however, we did not think that the transfusions were of material benefit.

Six cases of purpura were encountered in children under fifteen years of age; two of them died and two were improved when they left the hospital.

Excellent results following transfusion were obtained in two children suffering from acute purpura. A child, aged seven and a half years, had profuse nose bleeding and had vomited large quantities of blood (clinical diagnosis: morbus maculosus Werlhofii). Injections of horse serum were ineffectual, whereas one transfusion gave a marvellous result. The bleeding stopped immediately and the hemoglobin rose from 34 to 58 per cent. and the platelets increased to 104,000.

The other case presented a very rare condition, *i. e.*, acute purpura following chicken-pox. The boy, aged twelve years, had had chicken-pox, which seemed to run its normal course. On the tenth day of the disease all the pustules suddenly turned hemorrhagic. In addition he had profuse intestinal hemorrhages, which practically exsanguinated the boy. The condition was so serious that we had to transfuse him in the middle of the night. The father and mother were tested and the mother was used as donor. The boy seemed out of danger, when thirty-six hours later another profuse hemorrhage necessitated a second transfusion, the blood being taken from an aunt. Though the boy's life seemed to be ebbing away, this transfusion saved him. Bleeding stopped entirely and he made an uneventful recovery.

Transfusion results in purpura in the adult male were very unsatisfactory. One case made a very excellent recovery, two died in the hospital, whereas the others left the hospital upon request soon after the transfusion, without real improvement.

(c) *Gastro-intestinal Hemorrhage* (11 *Cases*, 20 *Transfusions*; 2 *Cures*, 1 *Improved*, 8 *Deaths*).

Hemorrhages from the gastro-intestinal tract are a very frequent indication for blood transfusion. Gastric hemorrhages especially often reach such alarming proportions that transfusion must immediately be resorted to. The prognosis depends entirely upon the causative factor of the hemorrhage. If we are dealing with an ulcer of the stomach an operation should be performed immediately after the transfusion. The combination of transfusion and immediate gastric operation gives very good clinical results. Cases of this character do not appear in this group but are reviewed in a subsequent chapter on preoperative transfusions.

However, it would be erroneous to assume, as is often done, that

the cause for a profuse gastric hemorrhage must necessarily be an ulcerative process in the stomach. It should not be overlooked that the real cause for a gastric hemorrhage is very often extragastric (spleen, liver, appendix, esophagus, etc.). In these cases an exploration of the stomach fails to show any pathological changes. We encountered two such cases, with negative stomach findings, on exploration. Both these cases have been previously reported by Dr. Moschcowitz.[36] One of them, a nurse, made an uneventful recovery. She has been perfectly well for three years. The cause of her most alarming hemorrhages has never been established. The other case, a child, received eleven transfusions (five of them by the citrate method) in the course of three years, on account of repeated and very profuse gastric hemorrhages. Exploration of the stomach was entirely negative. The hemorrhages persisted and recurred at intervals of from three to six months. In the latter part of her illness the spleen showed considerable enlargement, thus giving the first clue as to the real cause of the hemorrhages. Postmortem examination showed that the child had been suffering from Banti's disease. Splenectomy, as described by Balfour, would have been the only proper procedure to cure this little girl. However, when the diagnosis was made she was in such a weakened condition that operative interference was out of the question. It is evident that the transfusions could give only temporary relief. In another case, cirrhosis of the liver was the evident cause of the gastric hemorrhage. Transfusion was done as a last resort, but did not change the ultimate fatal outcome.

Three cases with a typical ulcer history of some years' duration and sudden very profuse hemorrhages required transfusion. The decision as to when to transfuse these cases is not an easy one. Many of the older text-books advise not to replace the lost amounts of blood by any intravenous injection. They claimed that a very low blood-pressure was necessary to give the ulcer a chance to heal and that a patient with a bleeding ulcer must be practically exsanguinated before he could recover. They maintained that a gastric hemorrhage, alarming as it may seem at the moment, will not cause death, but always stops automatically. This assumption, however, is incorrect. It cannot be denied that some patients will recover spontaneously even after very profuse hemorrhages. However, it is not safe to wait too long, on the assumption that Nature will take its course and safeguard an ultimate recovery. Death from gastric hemorrhage is by no means infrequent. If the blood-pressure falls below 80 mm., if the patient's lips become white or livid and his pulse becomes very rapid, an immediate transfusion followed by an operation, if possible, becomes extremely urgent. The combination of transfusion and operation offers the best

[36] Massive Hemorrhages from the Stomach without Demonstrable Ulcer, Am. Journ. Med. Sc., 1916, cli, p. 714.

chances for absolute recovery. We lost two cases in spite of repeated transfusions, because we hesitated to explore immediately on account of the general condition of the patient. The hemorrhages recurred and the patients, who seemed to have been materially improved after the transfusions, died suddenly from recurrent hemorrhages before the source of the bleeding could be properly attacked.

One case seemed perfectly well after three transfusions, without recurrence of bleeding and with loss of all gastric symptoms (observation time four weeks). It is impossible to fix any definite rules about transfusion in hemorrhages. However, it seems that Bernheim's[37] advice is a very wise one: "When in doubt, transfuse." Nothing is lost and a great deal may be gained by a transfusion given at the proper moment.

In one case of inoperable gastric carcinoma with profuse hemorrhages, the bleeding stopped after one transfusion and the patient left the hospital temporarily improved.

We had three cases of intestinal hemorrhages. The first case was suffering from ulcerative colitis. Neither repeated transfusions nor a colostomy stopped the hemorrhages and the patient died. The other two cases were severe cases of typhoid with profuse hemorrhages. Transfusions stopped the hemorrhages, but both cases died ultimately from sepsis.

(*d*) *Cholemia* (5 *Cases*, 11 *Transfusions;* 5 *Deaths*).

Transfusion of blood in cases of jaundice is a very efficient and frequently applied remedy. As a preoperative measure it will materially increase the patient's chances for a speedy recovery. Applied postoperatively, to combat alarming oozing from the wound, it will often stop the hemorrhages like magic. The reason why we had 100 per cent. mortality in this group is based upon the fact that we were dealing with very complicated cases, not with cases of simple jaundice, caused by a common-duct stone.

Case 1: Common-duct stone; choledochotomy; secondary gastro-enterostomy for periduodenal adhesions.

Case 2: Biliary fistula following pylorectomy and gastro-enterostomy; second operation: drainage of common duct; third operation: cholecystoduodenostomy.

Case 3: Choledochotomy; biliary fistula; choledochoduodenostomy.

Case 4: Congenital stenosis of common duct in a child; cholecystostomy; bleeding from mouth, gums, rectum (hemorrhagic diathesis); five transfusions; temporary improvement; death.

Case 5: Hepaticoduodenostomy for common duct obstruction.

[37] Limits of Bleeding Considered from the Clinical Standpoint, Am. Jour. Med. Sc., 1917, cliii, p. 575.

Transfusions were very beneficial in every one of these cases. However, the lives could not be saved, as the very complicated surgical procedures failed to establish normal anatomical conditions, thus causing ultimate death.

(*e*) *Postoperative Hemorrhages* (13 *Cases*, 16 *Transfusions*; 6 *Cures*, 7 *Deaths*).

We have collected in this group those cases in which hemorrhage followed operative interference and was entirely due to the trauma incidental to the operation (imperfect primary hemostasis, secondary hemorrhage, etc.).

Hemorrhage is not infrequent as a postoperative complication in gastric surgery, not only in cases of resection, but occasionally in simple gastro-enterostomies. An immediate transfusion of blood may save the life of the patient. We had two such cases, one following a partial resection of the stomach for ulcer of the lesser curvature and the other following a gastro-enterostomy. Both patients were in most serious condition and practically pulseless when the transfusion was given, and both made a rapid and uneventful recovery. In five cases (three ulcers and two carcinomata) transfusion was of temporary benefit only and did not prevent a fatal outcome.

Two patients with hemorrhages following operation on the genito-urinary tract were cured by transfusion, one occurring on the thirty-eighth day following a nephrectomy for tuberculous pyonephrosis. The wound which had been sluggish and necrotic assumed very soon after the transfusion a normal aspect and the patient's recovery was a rapid one.

Two children had profuse hemorrhages following operations for osteomyelitis of the femur; one of them was cured.

Two transfusions were given, with good result, in a nasal hemorrhage following resection of the turbinate bone.

In a case of profuse hemorrhage following an incision of a pylephlebitic liver abscess the bleeding stopped following the transfusion. However, the boy died a few days later from the primary condition.

(*f*) *Hemorrhages from the Female Genital Organs* (2 *Cases*, 2 *Transfusions*; 2 *Deaths*).

The importance of blood transfusion in ruptured ectopic pregnancy is by no means negligible, though our series has one case only. In cases of sudden profuse hemorrhages blood transfusion ought to be resorted to contemporaneously with immediate operation. While the surgeon is stopping the hemorrhage, new blood should be introduced into the circulation. The mortality can thus be reduced materially. It would be unwise, for obvious reasons, to introduce the blood

before the operation. Transfusion can only be effective after the bleeding vessels have been properly tied. The cause of death in our case was imperfect hemostasis.

The second case died from profuse operative hemorrhage based on a chorioepithelioma. The enormous bleeding was unexpected, no donor was at hand and a colleague (Dr. London) who happened to be present at the operation acted as donor.

(*g*) *Traumatic Hemorrhages* (2 *Cases*, 3 *Transfusions;* 1 *Cure*, 1 *Death*).

We encountered only two cases of hemorrhages following severe trauma. The subject of traumatic hemorrhage and its proper treatment has assumed vast proportions in the present war and has been extensively discussed in the last few years by a great many army surgeons. The reader is referred to those publications in which indications and results are discussed extensively, based upon an enormous material.

2. Diseases of the Blood.

(*a*) *Pernicious Anemia and Leukemia* (24 *Cases*, 39 *Transfusions;* 7 *Improved*, 4 *Not Improved*, 13 *Deaths*).

Up to the present time diseases of the blood were considered a very promising field for the application of blood transfusion. However, the results obtained are, if considered critically, very discouraging. Among 24 cases of pernicious anemia and different forms of leukemia (acute leukemia, acute myelogenous aleukemia, lymphatic leukemia, chronic leukemia, etc.), 13 died, 4 were not improved and 7 showed a temporary improvement. We have lately, based upon our own unsatisfactory experiences and those of others, discouraged the use of blood transfusion in all forms of leukemia. Temporary short improvement is usually followed by a rapid exacerbation of the disease.

Results obtained in pernicious anemia are somewhat better, as long remissions of comparatively good state of health can be obtained by repeated transfusions. However, blood transfusion in these cases can only be considered a temporizing, not a curative measure. Results obtained by blood transfusion in the early stages of the disease are often very promising and the intervals between remissions of rather long duration. However, the intervals get shorter and shorter, with the progress of the disease, and the efficiency of blood transfusion, even when resorted to frequently, decreases rapidly, while the disease runs its fatal course. Splenectomy has been of benefit in a few single instances only. The vast majority of cases succumb in the course of two years (and often in a much shorter period) in spite of transfusions or splenectomy.

(*b*) *Primary and Secondary Anemia* (*4 Cases, 7 Transfusions; 3 Cures, 1 Improved*).

Excellent results were obtained in the few cases of primary and secondary anemia which came under our observation. When they entered the hospital, the patients appeared to be desperately ill on account of the severe anemia. They made a rapid recovery after the transfusion.

3. Preoperative and Postoperative Transfusions (35 Cases, 39 Transfusions; 12 Cures, 23 Deaths).

Blood transfusion ought to be employed much more frequently as a preoperative and postoperative measure. Surgeons have in the last thirty years gradually widened their indications. Patients who are in a debilitated general condition ought to receive the benefit of a transfusion before they undergo large operations. They will stand the operative shock much better and their period of recovery will be shortened. In the same way a postoperative transfusion will often have the most marvellous effect. Instead of infusing large quantities of saline solution into the body, either subcutaneously or intravenously, a transfusion of blood ought to be given if alarming symptoms appear in the postoperative course. In fact, it is advisable to have a suitable donor available before the operation in case of emergency. It is not advisable, except in cases of profuse hemorrhage (ectopic pregnancy, etc.), to transfuse during the operation on account of the possibility of chills following the transfusion. It is an interesting fact that when blood is given following acute profuse hemorrhages chills do not occur.

By making extensive use of transfusions as a preoperative measure, eight patients, who were extremely bad operative risks, were saved. Among the fourteen deaths encountered in this series, 10 were based on the underlying condition, inasmuch as the operation revealed an inoperable malignant growth. By applying blood transfusion postoperatively, four lives were saved which were in extreme danger of passing away (empyema, acute mastoiditis, osteomyelitis of femur and pus kidney). The last case was in extreme condition following a simple incision and drainage of a pus kidney. 500 c.c. of blood taken from the husband of the patient changed the aspect entirely. She made an uneventful recovery not only from this operation, but from a subsequent nephrectomy.

Among the cases not saved were two lobectomies for lung abscess, one splenectomy for Gaucher's disease and one inoperable carcinoma of the liver.

4. Sepsis (5 Cases, 7 Transfusions; 5 Deaths).

The treatment of acute forms of sepsis by blood transfusion is a perfectly useless procedure and our experience of 100 per cent.

mortality coincides with those of other observers. Sad as these cases are we must recognize that transfusion will not alter the prognosis. Whether the use of blood from immunized donors, as suggested by Hooker,[38] will be of help, remains to be seen. There can be no doubt that the use of donors, who have acquired immune bodies by successfully combating the same disease previously, offers a somewhat hopeful outlook. However, the scarcity of these donors, especially as far as sepsis is concerned, will always stand in the way of its general usefulness. If anything can help an acute sepsis it must be done immediately. Time will be lacking to immunize a donor artificially. The use of blood of convalescent patients in the treatment of measles and typhus fever has been suggested by Ribadeau-Dumas and Brissaud[39] and Escluse.[40]

An occasional case of acute sepsis will recover automatically. I had occasion to observe such a case. A woman developed an acute bacteriemia with positive blood culture, following a gynecological operation. We were ready to transfuse her and held back at the last moment, because she was slightly improved. She made a somewhat stormy recovery and was perfectly well after a few weeks. If we had given her the transfusion as planned, we would naturally have concluded that transfusion had saved her life.

On the other hand, cases of subacute and chronic sepsis are very much benefited by blood transfusion, and results obtained by this procedure are often really marvellous.

5. Incurable Conditions (Transfusions Performed at Request of Family); (12 Cases, 12 Transfusions; 12 Deaths).

Transfusion has acquired such popularity among the laity that we are often forced to resort to it against our better judgment, in order to ease the mind of the sorrow-stricken family. We thus used transfusions in seven carcinomatous patients in the last stage, one case of third degree burns, admitted to the hospital in a dying condition, three cases of peritonitis and one case of sepsis, caused by an acute osteomyelitis of the femur.

6. General Debility (6 Cases, 8 Transfusions; 1 Improved, 1 Result Unknown, 4 Deaths).

Two cases of malnutrition in infants were tested as to the value of transfusion. We agree with other observers that transfusion does not help these little infants. They succumb to a serious disturbance of the metabolism in spite of the transfusions. Transfusions with

[38] Treatment of Staphylococcus Septicemia by Transfusion of Immune Blood, Ann. Surg., 1917, lxvi, p. 513.

[39] Transfusion in Measles, Bull. de la Soc. méd. des hôp. de Paris, 1918, xlii, p. 147.

[40] Essai de traitement du typhus exanthématique par injections intraveineuses de sang vivant de convalescent, retardé dans sa coagulation par citrate de soude Presse méd., 1915, xxiii, p. 450.

previous venesection were tried in 2 cases of acute nephritis. Results seem to be somewhat promising. However, the number of cases is too small to draw any definite conclusions.

7. Acute Poisoning (1 Case, 1 Transfusion; 1 Cure).

We had one brilliant result in a two-year-old boy who was admitted to the hospital in a dying condition, suffering from acute poisoning of unknown origin. He had slight air-hunger, showed extreme pallor and some purpuric spots on his legs and had passed bloody urine for twenty-four hours. Immediate transfusion saved his life. His hemoglobin rose from 15 to 50 per cent. following the introduction of 300 c.c. of blood taken from the father. His recovery was rapid and uneventful.

General Considerations. It is not advisable to advocate large transfusions. They may overstrain the heart and cause the death of the patient. Except in cases of profuse hemorrhage the average transfusions should range between 500 and 700 c.c. Very large ones are not more effectual clinically than medium-sized ones. Formerly large transfusions were quite en vogue. However, the simplicity of modern technic makes repetition of transfusion an easy matter and has replaced single large transfusions by repeated transfusions of medium size.

Nothing definite is known about the fate of the donor's blood after its introduction into the recipient. We do not know how long it preserves its own vitality nor when it is assimilated by the recipient's blood. That in a great many instances it acts as a stimulant for the blood-producing organs of the recipient can be seen from the fact that many cases show a rapid automatic rise of the hemoglobin a few days after the transfusion. This result is obtained just as effectively by medium-sized as by large transfusions.

The general popularity which the citrate method has acquired in the last year makes it unnecessary to enter into long discussions as to the relative values of citrated blood to non-citrated blood. It has been established beyond doubt that the clinical efficiency of the citrate method is absolutely equal to any other method of blood transfusion. Many authors have tested the relative values of the different methods by using various methods on the same patient (Bernheim,[1] Garbat,[2] author, etc.), and have shown that results obtained by the citrate method are just as good as those obtained by the older and more complicated methods.

It seems hardly fair to group the other methods as methods applying pure, unmodified blood, as has been done by some authors, in contradistinction to the citrate method. Citrated blood is just as

[1] Sodium Citrate Blood Transfusion. A comparison. Jour. Am. Med. Assn., 1917, 69, 359.

[2] Sodium Citrate Transfusions. A study of 100 cases. Jour. Am. Med. Assn., 1919, 72, 1.

pure as non-citrated blood. One of the most efficient and life-saving qualities of the blood is its tendency to coagulate. The possibility of existence of the human being is based on this fact. However, it was just this coagulation tendency of the blood which stood in the way of a development of a simple technic for blood transfusion. There can be no doubt that during the transfer of blood from donor to recipient the coagulation tendency of the blood is useless and unnecessary. The effectiveness of sodium citrate is based upon the fact that it changes temporarily during the transfusion this coagulating tendency of the blood without changing any of its other qualities.

The amounts of sodium citrate used with this method are so small that they do not play any role in the chemical and clinical properties of the recipient's blood. "Even after profuse hemorrhage there is enough calcium left in the bloodvessels and in the lymph for re-establishment of coagulation conditions in the transfused blood" (Sabattani[43]). In other words, the mixture of sodium citrate is efficient as anticoagulant only while the blood is outside the body. Soon after its introduction into the recipient the coagulating efficiency of the transfused blood is fully reëstablished. It is probable that the sodium citrate is either changed or rapidly excreted by the kidneys.

The frequency of chills following transfusion does not seem to vary much according to the different methods used. In a series of 280 transfusions, Meleney, Stearns, Fortuine and Ferry[44] observed the same percentage of reactions with the citrate method as with the syringe-cannula method. They conclude that the method of transfusion has nothing to do with the occurrence of the reaction.

According to the experience of the author and of others, chills occur somewhat more frequently with the citrate method than with other methods of blood transfusion. In our series of 200 transfusions we encountered chills in 40 cases (20 per cent.). The reasons for these chills, if proper blood tests were made before the transfusion, are not quite clear. I have repeatedly seen that in the same person citrate transfusions did not cause any chills, whereas subsequent transfusions of non-citrated blood caused acute rise of temperature with chills, and *vice versa*.

It is interesting to note that in the first 22 tranfusions of our series no chill occurred. Furthermore, I have never observed a chill following transfusion given to children, even when rather large amounts of blood, as compared to the body weight, were introduced. No chill was encountered in any of those cases in which transfusion was given following a profuse hemorrhage.

It is by no means impossible that future investigators may find

[43] Calcium and citrate trisodique dans la coagulation du sang, de la lymphe et du lait, Attidella R. Accademia della Sc. de Torino, 1900, 36.

[44] Post-transfusion Reactions, Am. Jour. Med. Sc., 1917, cliv, p. 733.

another anticoagulant which may possibly diminish the percentage of chills. However, it is safe to say that the principle of the method (application of an anticoagulant for the simplification of the technic of blood transfusion) will prove of permanent value. The application of this principle has transformed transfusion from a very cumbersome and difficult method into a most simple procedure. Blood transfusion at the present time is not any more in the hands of a few specialists, but within the reach of every practitioner. By the immediate application of this simple method of blood transfusion in emergency cases a great many lives can be saved, especially in small communities, where the performance of the older, more complicated methods was out of question.

A REPORT OF THE PATHOLOGICAL CHANGES OF THE BRAIN IN 162 CASES OF PARESIS.

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The pathological changes of the brain and meninges found in paresis are based on 162 postmortem examinations on cases of paresis performed at the Norristown State Hospital. The diagnoses of the cases are from the clinical records and the diagnoses are based on careful histories, physical and mental examinations, and the more recent cases on the recently developed study of the blood and spinal fluid—as the cell count, Alzheimer's method for differential count, Noguchi's, Pandy's and Nonne's tests for protein content in the fluid, the Wassermann test on the blood and cerebrospinal fluid and the Lange colloidal gold test. By the routine use of these methods errors in differential diagnosis between cerebral syphilis and non-specific disorders are practically impossible.

The more recent cases of autopsies that have been diagnosed as paresis show 100 per cent. of positive Wassermann tests on the blood and spinal fluids. Plaut[1] describes two negatives among 320 sera, practically 100 per cent. positive, while in 276 cerebrospinal fluids 9 were negative and 96 per cent. positive. Boas found the Wassermann reaction positive in 100 per cent. of 243 cases. Ross and Jones[2] found their reaction positive in all their cases of paresis. Turner[3] examined 78 cases and found a negative reaction in 2 cases only. Boyd[4] found 8 positive reactions in 8 cases. Fildes and McIntosh[5] found the Wassermann positive in 98 per cent. of the cases of paresis. Among 143 cases of paresis, Lowery[6] found the

[1] Ztschr. f. d. ges. Neurol. u. Psychiat., original, 1911.
[2] British Med. Jour., 1909, i, p. 1111.
[3] Jour. Ment. Sc., 1910, lvi, p. 485.
[4] Ibid., 1912, lviii, p. 203.
[5] Syphilis from the Modern Standpoint, London, 1911, p. 117.
[6] Am. Jour. Insanity, April, 1916, lxxii.

blood test positive in 87.5 per cent. and negative in 10.3 per cent. Noguchi compiled the results of 26 different observers, who found positive serum reactions in 84.5 per cent. of 660 cases and 91 per cent. findings in 481 spinal fluid examinations. These percentages are probably below the correct findings unless examinations of the serum on fluid were made at repeated intervals, as in all the cases of undoubted paresis it has been my experience to find 1 or 4 of the 4 tests positive while most gave all 4 tests positive. The current literature contains many references and reports upon this subject. In most of the cases examined by the writer the typical Wassermann reaction was found present, which Kaplan[7] refers to as the "Wassermann-fast" phenomenon.

Generally speaking, the findings thus observed are in advanced cases, some extending over many years, with periods of remission. Among these cases some have been found which have shown a combination of paresis with other specific lesions. Probably none of the findings in paresis are pathognomonic, as the pathology found is due to irritating agents, and in these cases it is supposed to be due to the Treponema pallidum. It seems that an inflammatory process is behind every form of syphilitic involvement and that the spirochetes are at the bottom of the reaction. When a spirochete, as shown by Noguchi and Moore,[8] appears in the nervous tissues there is a double reaction: (1) of the nerve cells (parenchyma) and neuroglia (fixed interstitial cells) and (2) of the wandering cells. The inflammatory reaction is in direct proportion to the kind of tissue involved. There is every reason why the meninges respond more violently than the parenchyma of the brain. The reaction of vascular interstitial tissue will be of a different nature from that of parenchymatous tissue. Lymph and plasma infiltration and mast cells are the fundamental characteristics of the reaction caused by the spirochetes. Orton[9] says it is this association of plasma cells, then, in the perivascular spaces, and especially when they occur as a close-packed mosaic of angular forms around the smaller capillaries, the so-called "mantle infiltration," that forms the histological criterion, without which the diagnosis of paresis can scarcely be considered as established. Generally speaking, the spirochetes produce the same histological pathology as in other tissues. We find that paresis and tabes are anatomically just as cerebral and spinal, and the pathology is based in all cases on a similar reaction to the same agent. The reaction[10] to the injury of the spirochetes in the meninges is the proliferation of fibroblasts to replace those of adjoining fibroblasts which have been destroyed. The cortical cells are killed

[7] New York Med. Jour., August 29, 1914, p. 358.
[8] Jour. Exp. Med., February 1, 1913, xvii, p. 232.
[9] Am. Jour. Insanity, July, 1916, lxiii, p. 91.
[10] Mallory: Principles of Pathological Histology, 1914.

slowly and diffusely here and there, and therefore the regeneration is diffuse. This reaction takes place slowly, as seen from the slow downward development of the case. The process in the meninges is chiefly confined to the bloodvessels, and they are filled with endothelial leukocytes which occlude the lumen, thereby causing necrosis, which is later replaced with calcium producing the cranial osteosclerosis, as found in 42 per cent. of the cases. These are evidently cases of long standing.

Quite a number of sections were made from several brains to demonstrate the presence of Treponema pallidum, with positive findings in only two sections. Levaditi's method was used. Noguchi,[11] in 1913, succeeded in finding the Treponema pallidum in 12 out of 70 specimens from the brains of paretics, and his findings were confirmed later by many observers. Foster[12] studied material from brain puncture from a series of 61 paretics by the dark-field illumination method and found active spirochetes in 27 cases (44 per cent.). Spirochetes have also been found in the cord and cerebrospinal fluid. These findings seem to prove Kraeplin's assertion: "We can today declare with the greatest certainty that syphilitic infection is necessary for the later appearance of paresis." Noguchi's discovery furnishes the fact hitherto wanting to complete the chain of evidence and demonstrates that paresis, as long held by Dunlap, is merely a late manifestation of syphilis, though presenting a somewhat different pathological picture from that seen in the hitherto recognized specific cerebral disorders which have been grouped by Nonne under three headings:

1. Syphilitic new growths.
2. Chronic hypoplasia inflammation.
3. Disease of the bloodvessels.

We can now add to the category paresis and tabes dorsalis, formerly the so-called parasyphilitic diseases.

Sections for microscopic study were taken from some of the brains and fixed in 10 per cent. formalin and some in Müller's fluid. The staining was done by Marchi's method for neuroglia, hematoxylin and eosin stains and concentrated aqueous solution of thionin. Sections were taken from the frontal, precentral and occipital cortex and infiltrated with paraffin and stained with the above methods. The findings in general were as follows: The nerve cells of the cortex were found to be in all stages of degeneration—shrinkage and disintegration. Many of the cells were absent. Some had lost the protoplasmic process and some the axon fibers. On account of the nerve cells being disarranged the normal layers of the cortex were confused and could not be made out. The tangential associa-

[11] Jour. Exp. Med., February 1, 1913, xvii, p. 232.
[12] Allg. Ztschr. f. d. Psychiat., Band lxxi, Heft 6.

tion fibers and collaterals were greatly reduced in proportion. As a result of this the cerebral convolutions were shrunken and fell apart and we have cerebral cortical atrophy, with widened sulci, as found in 54 per cent. of the cases.

Most of the brains examined have been hardened in formalin and were not sectioned until thoroughly hardened.

These 162 autopsies are among 1714 autopsies, thereby constituting 9.3 per cent. Among these 162 there were 124 males and 38 females. Out of the entire number there were only 9 negroes. The average age of death is forty-eight years, the male average being forty-nine years and the female average forty-three years. The oldest male case was sixty-two years and the youngest thirty years; the oldest female was sixty-one years and the youngest twenty-six years.

In the 162 cases of paresis the average weight of brain is 1190.5 grams, the lightest being 820 grams and the heaviest 1680 grams. The average weights of normal brains, according to race, were as follows:[13]

	Grams.
Caucasian	1335
Chinese	1332
Sandwich Island	1303
Malay and Indian	1266
Negro	1244
Australian	1185

The average English and American brain weighs 1346 grams.

The pathological findings in 162 cases of paresis and the percentage of each finding are summarized as follows:

	Per cent.
Chronic leptomeningitis	100
Chronic pachymeningitis	81
Hydrops meningeus	72
Cranial ependymal sclerosis	71
Dilated cerebral lateral ventricles	60
Cerebral cortical atrophy	54
Cerebral arteriosclerosis	43
Cranial osteosclerosis	42
Cystic choroid plexuses	33
Chronic internal hemorrhagic pachymeningitis	17
Pachycephalitis	14
Cerebral softening and edema	14
Cerebral congestion	10
Chronic external and internal adhesive leptomeningitis	8
Dilated fourth ventricle	5
Coherent cerebral hemispheres	4
Softening of velum interpositum	3
Small thrombotic lenticular softenings	3
Cerebral edema and softening	2
Cystic and cheesy degeneration of choroid plexuses	2
General cerebral atrophy and sclerosis	2
Thrombotic softening of lenticular nucleus close to the posterior limb of the internal capsule	2
Old area of thrombotic softening of both caudate nuclei	2

[13] Emil Villiger's Brain and Spinal Cord, 1912, 3d ed.

Findings appearing only once in the series are as follows:

Congested and thickened velum interpositum and softened pituitary body.
Chronic adhesive pericranitis.
Dilated third ventricle.
Cerebral hemorrhage.
Dilated cerebral perivascular lymph space.
Cerebellar tumor.
Thrombotic softening of right caudate nucleus and part of anterior and posterior limbs of the internal capsule.
Calcification of falx cerebri.
Small perivascular cerebral and cerebellar softenings.
Tuberculoma of dura.
Old hemorrhage of the right caudate nucleus.
Thrombotic softening of the left putamen of the lenticular nucleus.
Thrombosis of the right anastomotic vein of Trolaid.
Cyst of the pia and arachnoid.
Softening of the left cerebellar hemisphere involving the lobus semilunaris, lobus postero-inferior, lobus quadrangularis from thrombosis of the left vertebral and of the left postero-inferior cerebral arteries.
Thrombotic softening of the posterior limb of the right internal capsule.
Calcified nodules of the left temporal pole.
Spindle-celled sarcoma of the right optic thalamus.
Absence of middle commissure of optic thalamus.
Small thrombotic cortical softenings of left cerebellum and right occipital lobes.
Anamolus anterior cerebral arteries.
Thrombosis of the right lateral and superior longitudinal sinus.
Thrombotic softening of right lenticular nucleus and double optic atrophy.
Thrombotic softening of the left cerebellar white tracts.

The microscopic findings were practically similar in the cases examined and consist of the following in general:

Syphilitic perivascular round and plasma cell exudate.
Distortion of cerebral cortical layers.
Chronic ganglia cell degenerative changes and cerebral gliosis.
Acute and chronic degenerative ganglia cell changes with atrophy.
Endarteritis and pericarditis.

A careful study of the pathological processes that have taken place in the brain of paretics will have an important bearing upon the treatment of syphilis. Quite a few men have reported improvement in cases of paresis with various forms of treatment. One goes so far as to make the remark that "I am still looking for *cures* in paresis." Cotton[14] gave antisyphilitic treatment to 66 cases of paresis, and his results were that out of the 66 he had 11 cases which he recorded as arrested and 7 much improved, but none cured. It will be recognized that antisyphilitic treatment can have no direct effects upon degenerating nerve structures, and therefore upon the symptoms and signs of paresis; nevertheless, it may prevent the occurrence of further reaction in other areas by killing the spirochetes. Even among the early cases of paresis which have been autopsied there is a considerable amount of nerve-cell destruction, and it is evident that there must be considerable damage to the brain before mental symptoms are apparent. In the advanced case the cell destruction is so marked that even if treatment could remove the spirochetes a large amount of mental defect would remain.

[14] Am. Jour. Insanity, July, 1915, lxxii, p. 150.

REVIEWS

MEDICAL WAR MANUAL NO. 7. MILITARY SURGERY OF THE ZONE OF THE ADVANCE. By GEORGE DE TARNOWSKY, Major, M. C., U. S. R., American Expeditionary Forces. Pp. 330; 36 illustrations. Philadelphia and New York: Lea & Febiger, 1918.

THIS small manual was prepared under the supervision of the Surgeon-General and the Council of National Defense for the guidance of medical officers working in the zone of the advance, and is remarkable for the amount of up-to-date necessary information confined within its covers. Its essential aim is to give a résumé of the primary treatment which has proved most satisfactory in the opinion of those best qualified to judge. Not only to those in actual service is it valuable, but to every physician who wishes to familiarize himself, with small effort, with the best the war has produced, on the Allied side, in the alleviation of the sick and wounded. Its description of the various activities of the medical man in the most interesting field of the war, the zone of the advance, may fairly be said to be fascinating. T. T. T.

BIPP TREATMENT OF WAR WOUNDS. By RUTHERFORD MORISON, Professor of Surgery, Durham University. Pp. 67; 9 illustrations. London: Henry Frowde and Hodder & Stoughton, 1918.

MORISON'S contribution to the treatment of war wounds has been properly classed with the great discoveries in war surgery. It has been used widely, particularly by Englishmen, and the reported results have been very encouraging. This little book by the discoverer of the method describes it concisely and clearly and gives the various uses to which it has been applied with much credit to itself and the author. The name "bipp" was derived from the combination of the first letters of the name of each of its constituents, bismuth—iodoform—paraffin, with that of the word paste. The walls of the wound or abscess cavity having been cleaned thoroughly, a thin layer of the paste is smeared over the whole surface and the cavity closed completely by sutures, when possible, otherwise it is treated as an open wound. T. T. T.

"TRENCH FEVER." REPORT OF AMERICAN RED CROSS RESEARCH COMMITTEE. Oxford University Press, 1918.

THE report is delivered in a 446-page, cloth-bound, super-royal octavo volume, well illustrated by charts and half-tones and plentifully interspersed with tables.

The commission consisted of Majors Richard P. Strong, Homer F. Swift and Eugene L. Opie and Captains Ward J. MacNeal, Walter Baetjer, A. M. Pappenheimer and A. D. Peacock. To these Lieutenant David Rappoport was subsequently attached. Of these officers all were Americans except Captain Peacock, and while much assistance was rendered by the British authorities in furnishing material and quarters, the work was conducted, with this exception, entirely by American agencies.

It appears as though the laboratory and other facilities were superior to those obtaining in many other lines of activity on the front, and this, coupled with the evident thorough organization of the personnel, has made possible the rich detail and preservation of minute records which are so refreshing to the scientific reader. One of the most impressive phases of the presentation is the able editing by Major Strong.

The research was directed particularly to the question of transmission because this phase was the most important in prevention, and so in conservation of man-power to the armies.

Points as to etiology are recorded only because they resulted from the main line of investigation.

Inasmuch as the disease is not transmissible to lower animals, American volunteers were used where such were necessary. Of these, 82 were selected out of several hundred offering themselves. In some respects the investigation parallels that of the Yellow Fever Commission of eighteen, and may well be considered as one of the finest pieces of American research conducted since that time.

Clinical Features of Trench Fever. These are particularly valuable from this source because they come from *known* cases of "pure-bred" trench fever, and the symptoms and signs, therefore, that are assigned to the disease cannot be questioned on the basis that they are those of some other P. U. O. (pyrexia of undetermined origin).

Prodromes was present in only two-thirds of the cases, consisting of headache generally one day before the onset; but in some cases headache and body pains antedated it by a week to ten days.

The onset is sudden, with more marked headache, chill and sudden temperature rise to 103° and 104°, great prostration and weakness. Most important in diagnosis is the tenderness which accompanies the frontal and postorbital headache, and the lumbar, thigh and calf pains. The spleen was not enlarged in 25 per cent. of the cases on the first day. A macular eruption similar to that of typhoid fever appears in 50 per cent. of the cases by the second day.

The course extended over a period of from one to several weeks, showing regular to irregular relapses of one or two days, with complete intermission of four or five days. The temperature rises suddenly to 103° or 104° in the exacerbations and suddenly drops in a day or two. Leukocytosis was found so variable as to offer no aid to diagnosis.

In short, the features common to many acute infections are present. "When trench fever assumes certain forms it is quite characteristic; when it assumes others it can only be diagnosed by taking all its positive features into consideration and by ruling out other diseases." And "In contradistinction to the ordinary infectious disease, trench fever is characterized by its tendency to relapse, by freedom from symptoms and signs between the relapses, in many cases by long persistence of the infection and in a few cases by distinct relapses, with long periods of apparent normality."

The need for laboratory aids in diagnosis is very evident in the doubtful cases and brings home to us what real advances have been made along these lines in the older and better-known infections.

The following conclusions were reached by the commission as the result of their experimental work.

1. That trench fever is a specific infectious disease; that it is not a modified form of typhoid or paratyphoid fever and is not related from an etiological standpoint to these diseases.

2. That the organism causing the disease is a resistant filterable virus.

3. That the virus causing trench fever is present particularly in the plasma of the blood of trench fever cases, and that such plasma will produce the disease on inoculation into healthy individuals.

4. That the disease is transmitted naturally by the louse (Pediculus humanus, Linn., var. corporis), and that this is the important and common means of transmission. That the louse may transmit the disease by its bite alone, the usual manner of infection, or the disease may be produced artificially by scarifying the skin and rubbing in a small amount of the infected louse excrement.

5. That a man may be entirely free from lice at the time he develops trench fever, the louse that infected him having left some time previously as its host, and that the louse need only remain upon the individual for a short time in order to infect him.

6. That the virus of trench fever is also sometimes present in the urine of trench fever cases and occasionally in the sputum, and that the disease may be produced in man by the introduction of the virus in the urine or sputum through the scarified or otherwise abraded skin.

7. That since the urine and sometimes the sputum of trench fever patients are infective, these should be sterilized in order to avoid the possibility of accidental infection from them.

8. That in order to prevent trench fever or limit its spread, and

thus save man-power for the armies, greater efforts must be made to keep soldiers in general from infestation with lice.

The above conclusions were reached on the basis of the following (among other) findings:

Blood from trench fever cases inoculated into mice, white rats and guinea-pigs yielded no typhoid organisms in the animal.

Blood, urine and feces cultures from trench fever cases at different stages of the disease resulted negatively for the typhoid group of organisms.

The agglutination titer in trench fever (after the method of Dreyer) did not correspond to that of a typhoid group infection following antityphoid vaccination.

The virus resists 60° C. moist heat for thirty minutes, but is killed by 70° C. moist heat for thirty minutes.

The virus is not killed by drying (urine, louse excrement).

Trench fever urine filtrate (Chamberland L. unglazed porcelain) produced the disease in one out of two volunteers inoculated.

Saline suspension of louse feces similarly filtered produced the disease in two out of three men inoculated.

Twenty-three men out of thirty-four inoculated intravenously with trench fever *plasma* contracted trench fever. Whole blood and clear unfiltered plasma contained most of the virus (23 out of 25 trials; washed erythrocytes little or none, 4 trials).

The virus is therefore probably not intracellular.

Filtered plasma was not infectious, probably on account of the colloid of the serum obstructing the pores of the filter (6 trials).

The incubation period varied between five and twenty days, depending on the stage of the disease at which the blood was taken.

In testing the following louse transmissions, thirty-eight men were used.

Twenty out of twenty-six men artificially infested with trench fever lice developed trench fever.

Five men out of five tested were infected by the *bite* alone.

Eight men were infected by scarifying the skin and rubbing in trench fever louse excrement.

In the above louse experiments it was found that lice may remain infective for *at least* thirteen days.

The inoculation period in louse-bitten cases is from fifteen to thirty-eight days, with an average of twenty-one days.

Two men bitten by hundreds (1500) of offspring of trench fever lice did not contract the disease. That is, the virus is not hereditary in the louse. The commission evidently inclines to the belief, without so stating definitely, that the virus has a life-cycle in the louse. This is suggested by the longer incubation period of trench fever by *louse* transmission than by direct *blood* inoculation, but the committee guards its opinion by granting that the longer period could also be explained by the smaller amount of virus inoculated. To

this the reviewer would add that the virus might also be biologically modified by its habitat in the louse in such a way (reduction of virulence) that it would take the longer time to produce the onset of the disease, and that certainly the louse is not an obligate intermediate host at all stages of its life-cycle (if it has one), as shown by successful direct blood transmission.

Conclusion No. 7 is important in regard to camp sanitation. Because the subject carries no lice and appears healthy is no reason why he may not be in the incubative stage of the disease.

Attempts to infect with trench fever *feces* failed (three trials).

One man out of three was infected by rubbing trench fever sputum into scarified skin.

Five out of eight were infected by dried (one week) urinary sediment from trench fever cases.

The war is now over and the research loses, with it, much of its surface glamor and does not urge upon us as it would have done a year ago. But it has rendered services which are permanent. It has established, first, the series of facts enumerated above regarding the titular subject, trench fever. In the second place it has further incriminated the already convicted louse and indicates that here we may expectantly inquire for a few (or more) other morbid potentialities in this parasite which the world war did not bring out. In the third place it shows that systematic, correlated, refined, properly controlled and minutely reported research *can* be done (in spite of field difficulties) when systematically prearranged by some central organization like the American Red Cross, Public Health Service or like body. And, finally, we find that when the occasion arose there were, like Doctors Lazear, Carroll and other members of the Yellow Fever Commission, eighty-two American citizens ready to submit themselves to inoculation with a disease of unknown causation for the merely possible and unguaranteed benefit of their comrades-in-arms. W.

War Wounds of the Lung. By Pierre Duval, Chief Surgeon of Mobile Unit No. 21, of the French Army. Pp. 99; 27 illustrations. New York: William Wood & Co., 1918.

The recent war has been responsible for many valuable contributions to surgery, but very few have been more brilliant than those on the treatment of war wounds of the lungs, and of these none have been more revolutionary than the contributions of Duval. Early in the war he took the position that the let-alone treatment of lung wounds with grave complications, so generally followed at that time, should not prevail. He insisted that direct exposure, cleansing and suture of the wounds would save many cases that were then

dying. Since then his views have been widely accepted by the profession. This small volume is an epitome of his war work on the lung, and should be in the possession of every surgeon who would become familiar with the progress of lung surgery. When we recall how slowly and laboriously were developed the low-pressure chambers and high-pressure apparatus to prevent the supposedly dangerous collapse of the lung when the pleural cavity was opened, we realize how revolutionary was the surgeon who dared to open the chest widely without such aids, deliberately permit the lung to collapse, bring it out through the wound for inspection and manipulation, trim the ragged, devitalized wound surfaces, cleanse them and close the lung wound by sutures as any other wound, and after cleansing the pleural cavity replace the repaired lung within the thoracic cavity and hermetically close the chest wound. This brilliant conception carried through with great courage has met with remarkable success. T. T. T.

SURGICAL CLINICS OF CHICAGO. By NUMEROUS AUTHORS. Volume II, No. 3, June, 1918. Pp. 254; 63 illustrations. Philadelphia and London: W. B. Saunders Company, 1918.

URINARY calculi are discussed by Albert J. Ochsner, Kolischer and Eisenstaedt and gall-stones by Ochsner, Bevan and Smithies. The latter contributes an interesting study of 1000 cases of gall-stone bladder disease. Eisendrath's presentation of five cases of injuries of the thorax and his discussion of the progress made during the war in the surgery of the chest are very valuable, as are all the articles in this number of the *Surgical Clinics*. T. T. T.

MANUAL OF SPLINTS AND APPLIANCES FOR THE MEDICAL DEPARTMENT OF THE UNITED STATES ARMY. By Lieutenant-Colonel W. L. KELLER, M. C.; Major R. B. OSGOOD, M. R. C.; Major A. LAMBERT, M. R. C.; Major J. A. BLAKE, M. R. C.; Captain W. S. BAER, M. R. C., and N. ALLISON, M. R. C., Members of a Board Appointed for the Standardization of Surgical Appliances. Pp. 173; 43 illustrations. New York: Oxford University Press.

THE character of the contents of this very brief manual may be judged by its title and by the names of its authors. The splints and appliances were adopted because of their efficiency and correct mechanical principles, simplicity of design, low cost of construction and transportability. It is largely illustrative, with a brief general consideration of the whole subject and detailed description of the splints and appliances of the surgical dressings and accessory supplies. T. T. T.

AMPUTATION STUMPS: THEIR CARE AND AFTER-TREATMENT. By G. MARTIN HUGGINS, Medical Officer to the Government Schools. Pp. 21; 95 illustrations. London: Henry Frowde and Hodder & Stoughton, 1918.

THE author aims to supply a guide to the large number of surgeons engaged in treating cases in which amputation has been performed. There is great need of it because of the new amputation wound conditions resulting from the war. For example, the very severe wound infections characteristic of this war have led to more and more frequent employment of the guillotine amputations, by which term is meant all flapless, more or less circular amputations that are left open and unsutured to save life because of the presence of virulent sepsis. The fitting and selecting of suitable artificial limbs and appliances for various occupations receive much attention in the text and illustrations. The same is true of the complications frequently arising in connection with amputation stumps. T. T. T.

ESSENTIALS OF MATERIA MEDICA AND THERAPEUTICS (LIPPINCOTT'S NURSING MANUALS). By JOHN FOOTE, M.D., Associate Professor of Therapeutics, Georgetown University School of Medicine. Pp. 310. Philadelphia: J. B. Lippincott Company, 1918.

THE present edition is the third of this useful book for nurses. The number of remedies considered is purposely limited for simplicity and the principal classification is according to physiological action. The subject-matter is clearly written and with sufficient detail. The reviewer is familiar with no text-book that better suits the needs of nurses. Some little criticism may be made regarding the appended formulas, in view of the fact that nurses are so frequently tempted to prescribe, oftentimes to the discredit of medicine. The attempt to outline rules and formulas for infant feeding in two pages is poorly done. C. N. S.

MEDICAL CLINICS OF NORTH AMERICA, March, 1918. Volume I, Chicago Number. Philadelphia and London: W. B. Saunders Company, 1918.

IT is an appreciated opportunity to be taken with each issue of this publication to the clinics of well-known authorities to grasp their methods of analysis and to learn of their views on subjects of such general interest. The present volume takes us to the clinics

of Chicago. Dr. Charles Louis Mix has us consider some of the fundamental principles underlying the diagnosis of the more usual cardiac diseases. Dr. Solomon Strouse presents juvenile diabetes in twins; a case illustrating the Karrell treatment of edema and two cases showing the importance of details in the treatment of angina pectoris. Dr. Charles A. Elliott discusses the radium treatment of leukemia and presents one case with splenectomy. Dr. Frederick Tice refers briefly to epidemic respiratory infections. Dr. Charles Spencer Williamson presents a case of polycythemia. Dr. Milton Portis analyzes the differential diagnosis of lesions of the right upper quadrant of the abdomen, as evidenced by 8 cases. Dr. Arthur Elliott describes syphilis of the aorta; Dr. Joseph Freidman considers reflex gastric disturbance; Dr. Julius Hess, tuberculin skin reaction in childhood; Dr. Frank Wright, nephritis; Dr. Arthur Byfield, splenomegaly and cirrhosis of the liver; Dr. Ralph Hamill, insomnia and hysteria; Dr. Isaac Abt, asthma in children; Dr. Maximilian J. Hubeny, roentgen examination of the appendix; Dr. Henry Helmholz, pyelitis in the newborn. C. N. S.

PROTEOMORPHIC THEORY AND THE NEW MEDICINE. By HENRY SMITH WILLIAMS, B.Sc., M.D., LL.D. Pp. 304. Goodhue Company, 1918.

NEW theories and new applications of old theories are earnestly sought after by the medical profession, facing, as it does, problems pertaining to the cure of diseases that still await solution. The reviewer is, however, in doubt as to a suitable analysis of this work. It is certainly not presented after the fashion of our usual scientific treatises and undue emphasis is too frequently made to the originality of the author.

The study of proteins and anaphylaxis have, however, opened new viewpoints that bear on diagnosis and treatment of disease. The experiences, therefore, of any worker in this field may throw some light. Reference in this volume is made principally to the use of vegetable proteins, the author considering the proteins from alfalfa meal, alfalfa seeds and millet seeds most satisfactory. The injection of these proteins hypodermically in cancer subjects is claimed to alleviate pain, modify the discharge, modify the tumor itself and favorably influence the general health and mental attitude of the patients. The same proteins are observed to benefit markedly cases of (*a*) rheumatoid arthritis; (*b*) pulmonary tuberculosis; (*c*) pernicious anemia; (*d*) intestinal toxemia; (*e*) leukemia; (*f*) Graves's disease; (*g*) psoriasis; (*h*) asthma; (*i*) arteriosclerosis; (*j*) neurasthenia; (*k*) primary and secondary anemias.

The first part of the book is taken up with the theories involved, the blood changes noted and the mechanism of protein hydrolysis and immunization. The second part of the book has to do with observations as to the benefit derived from protein therapy. Unfortunately, what truths may be contained in its pages lose much of their appeal because of the manner of presentation. C. N. S.

INTERNATIONAL MEDICAL ANNUAL. A YEAR-BOOK OF TREATMENT AND PRACTITIONERS' INDEX. Thirty-sixth year. Pp. 666. New York: William Wood & Company, 1918.

THE reviewer has appreciated in previous years the merits of this synopsis of medical progress, and unhesitatingly commends this present edition as even surpassing the others in scope and selection of material. As a review of practical medical progress it is extremely useful, being easy of reference and adequately complete in detail.

In the present volume special emphasis is placed on the dictionary of remedies and treatment, including radioactivity and electrotherapeutics. Naturally, war injuries and war diseases are considered fully. The reviews are from as world-wide sources as the present medical literature permits. The wonder is that the contributors have been able to do as much as they have under the wartime conditions existing. C. N. S.

AIDS TO RATIONAL THERAPEUTICS. By RALPH WINNINGTON LEFTWICH, M. R. C. S., Eng. Pp. 233. New York: William Wood & Company, 1918.

A VOLUME small in size yet large when mesaured by the number of practical therapeutic suggestions filling its pages. A physician in the toils of a general practice appreciates in a book on therapeutics an author's clear-cut expression of his views and methods proved to his (the author's) satisfaction by actual experience. Such methods and views are here described, and while now and then they will run counter to the experiences of the reader, interpreted as they are meant, they will prove of great value.

Disregarding the time-honored custom of considering therapeutics in connection with diseases, classified according to the organs affected, he places in the same group all diseases which are of allied pathology and which require the same treatment. This undoubtedly avoids much repetition and impresses the essentials of group treatment, but for reference necessitates the use of the index, for certain diseases are properly considered under several various groups

according to the stage of the disease. There is more to be said in favor of the plan for the reviewing of therapeutics by general practitioners with experience back of them than for teaching therapeutics to under-graduates.

To give some idea of the manner in which the groupings are made a few of the forty-two chapters may be mentioned. He refers to the automatic habit group, the catarrhal group, the abscess group, the hemorrhagic group, the infective fever group, the intracranial pressure group, the colic group, etc.

His manner of therapy is indeed rational and thoroughly up-to-date, at least as much so as any one man can be in so many lines. He pleads for more extensive medical therapy used, with judgment, and favors many of the old measures that have been so thoroughly tested yet seem to be now discarded. He disputes the ground the surgeons take in considering appendicitis that all should come to operation.

The book is of no scientific value but would be a help to any general practitioner, though unfortunately many of the prescriptions contain drugs that are but slightly used in this country.

C. N. S.

GENITO-URINARY DISEASES AND SYPHILIS. By HENRY H. MORTON, M.D., Clinical Professor of Genito-urinary Diseases in the Long Island College Hospital. Fourth edition. Pp. 807; 330 illustrations and 36 full-page colored plates. St. Louis: C. V. Mosby Company, 1918.

THE fourth edition, revised and enlarged, of Morton's *Genito-urinary Diseases and Syphilis* from the press of a new publisher is a most commendable achievement and the work is destined to be a monument to the sterling judgment of the author. A careful review of the book evokes commendation for each chapter, and there exists little to criticise. The first forty chapters are devoted to the various diseases of the urological and genital tracts, including radiography, pyelography, cystoscopy, urethroscopy and tests of kidney function. It is noted that many of the cystoscopic and urethroscopic views are borrowed from other authors. Chapter XLI deals with chancroid and its complications. The wisdom of omission of the high-frequency and copper sulphate treatment of this disease might be questionable. Chapter XLII presents a consideration of erosive and gangrenous balanitis, the so-called fourth venereal disease. The remaining ten chapters are devoted to syphilis and are most commendable, the author concisely systematizing the subject and presenting the important points in a lucid and impressive manner.

So excellent are the chapters on chronic urethritis, prostatitis, seminal vesiculitis, urethral stricture, tumors of the bladder, urinary calculus, prostatic enlargement and diseases of the kidneys that minor criticisms appear ill-advised if not out of place. Nevertheless, the reviewer regards it as his duty to take exception to certain statements relative to the application and utility of indigocarmin as a functional kidney test, believing that its applicability is just as great in other diseases and conditions as in renal tuberculosis, in which particular disease its employment obviates the necessity of catheterization of the presumably normal ureter and kidney, a procedure not unattended with danger. He also disapproves of any illustration or description of Luy's segregation in a modern textbook on genito-urinary surgery. Exception might also be taken to the space devoted to the treatment of glandular hypospadias in comparison with that given to the penile and perineal forms of the malformation. It is unfortunate that more consideration is not given to the disposition of the uterer in nephrectomy for tuberculosis. It is observed that no mention is made of teratoma testis. The reviewer has had no personal experience with Ultzmann's brush apparatus in the treatment of old foci of inflammation in urethritis, but he deprecates the value of "sealing in" treatment to abort gonorrhea, astringent injections and the use of gonosan as an internal remedy superiôr to other substances commonly employed and less expensive. Due credit is due the publisher for the excellence of the illustrations and the type employed in this edition. B. A. T.

THE PREVENTION OF VENEREAL DISEASES. By OTTO MAY, A.M. (Cantab.), M. R. C. P., London; late Hon. Secretary National Council for Combating Venereal Diseases. Pp. 240. London: Oxford University Press and Hodder & Stoughton, 1918.

THIS timely topic is broadly dealt with by May from the standpoint of preventive medicine, the author particularly emphasizing the proved value of the application of local measures of prophylaxis or early treatment in the prevention or abortion of gonorrhea and syphilis. The importance of education in biology and the physiology of reproduction is regarded as a valuable aid in the elimination of venereal diseases, but its futility is recognized. Legislation aiming at the control of prostitution and vice has been and is still a recognized failure in the control of venereal diseases. The author justly concludes that personal prophylaxis or early treatment with the recognized drugs will accomplish more than other means in the prevention of venereal infections. W. H. M.

PROGRESS
OF
MEDICAL SCIENCE

THERAPEUTICS

UNDER THE CHARGE OF

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Prophylactic Value of Leary's Vaccine.—BARNES (*Jour. Am. Med. Assn.*, 1918, lxxi, 1899) describes the epidemic of influenza which developed at Wallum Lake, R. I. Of the population (225 patients and 94 employees) 25 per cent. were affected. Of the 114 young adults who were exposed to the disease, 40 per cent. developed influenza; 172 employees and patients were injected with prophylactic doses of an influenza vaccine furnished by Dr. Timothy Leary. However, the incidence of influenza was 20 per cent. among both the vaccinated and the unvaccinated. In 25 influenza cases following vaccination, 4 cases, or 16 per cent., died, and in 57 cases of influenza among the unvaccinated the mortality was 9, or 15.8 per cent. The conclusions drawn are that the morbidity was only slightly lower among the vaccinated and that the mortality among those developing influenza was practically the same whether vaccinated or not.

Experimental Study of Serum Therapy in Trichinosis.—From experiments on rats, HALL and WIGDOR (*Arch. Int. Med.*, 1918, xxii, 601) conclude that serum from animals convalescent from trichinosis when injected into other animals or fed to them mixed with trichinous meat does not prevent the development of trichinæ. However, the longevity data from these experiments, the clinical observations of Salzer, as well as theoretic considerations, lead them to believe that such a serum may be of decided value in combating the toxic features of trichinosis.

Effects of the Injections of Epinephrin in Soldiers with Irritable Heart.—PEABODY (*Jour. Am. Med. Assn.*, 1918, lxxi, 1912) and others have tested the effect of the injection of 0.5 c.c. of a 1 to 1000 solution of epinephrin in normal soldiers and in soldiers suffering from "irritable heart." In only one of the 27 control cases was there a suggestion of hypersusceptibility to epinephrin. In 65 patients the epinephrin

test was positive in 39, doubtful in 6 and negative in 19. The most important symptoms of the reaction were the presence of tremors, sweating, flushing, pulsation of peripheral bloodvessels, general nervousness and increase in blood-pressure, pulse-rate and depth of respiration. Furthermore, the "irritable heart" cases showed an increase in basal metabolism and in blood sugar more marked than in normal individuals. The electrocardiogram showed most constantly a slight decrease of the height of the *T*-wave. In individual cases other abnormalities were seen, such as increase of sinus arrhythmia, prolongation of *P–R* interval, partial heart-block, inversion of the *T*-wave and the production of ventricular extrasystoles. Peabody advises the use of epinephrin as an aid in the diagnosis of "irritable heart."

Contributions to the Physiology of the Stomach; Studies on the Control of Hunger by Drugs.—In this paper, GINSBURG and TUMPOWSKY (*Arch. Int. Med.*, 1918, xxii, 553) report the results of an investigation into the action of drugs on the hunger mechanism. Gastric fistulæ were produced in twelve dogs, and in four of these both vagi and splanchnics were cut ("isolated" stomachs). The drugs were usually administered subcutaneously in therapeutic doses. Atropin was found to inhibit gastric activity, counteracting the effect of pilocarpin and eserin (both of which increased the movements of the stomach, while the pulse-rate was coincidently diminished). Cocain caused a profound and lasting inhibition of gastric movements, which seemed less marked in the "isolated" stomachs. Camphorated oil was without effect when given subcutaneously; when administered intramuscularly a prolonged increase in activity was observed. Strychnin, in doses of $\frac{1}{90}$ to $\frac{1}{60}$ grain subcutaneously, increased gastric tonus, and at the same time there appeared to be a definite increase in the hunger contractions themselves. Direct application to Auerbach's ganglia also caused stimulation. The inhalation of 5-minim pearls of amyl nitrite caused only temporary inhibition of contractions; in animals with sectioned splanchnics and vagi, in addition to inhibition the tonus remained depressed for a long time, only gradually returning to its original level. Epinephrin intravenously caused a prompt and marked inhibition of the hunger contractions, lasting from one to two hours. Absorption from the raw surface of the fistula caused equally profound depression, but application to the nasal mucosa was without effect. Pituitrin is supposed to stimulate smooth muscle, regardless of its innervation, but in these experiments its action was remarkably like that of epinephrin, inhibition occurring immediately after subcutaneous injection. The duration of the effect, however, was much less. Other observers have noted that pituitary extracts may inhibit the movements and tonus of isolated intestinal loops. Ergot, administered intravenously, was usually followed by temporary inhibition of the gastric contractions, followed by lowered tonus and the resumption of the contractions. Intramuscular injection in one instance gave a tremendous step-like rise, with extremely high tonus, followed by a short rest and then another active period. No differences were noted in the response of the "isolated" and "intact" stomachs, except in the case of cocain, in which the action was less marked on the "isolated" stomach.

OBSTETRICS

UNDER THE CHARGE OF

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Rupture of the Uterus through the Cesarean Section Scar.—Novak (*Jour. Am. Med. Assn.*, July 13, 1918) states that in 1913 there had been reported 63 cases of rupture of the uterus through a Cesarean section scar. In 1916 this had increased to 74, and others have been reported. His own case is as follows: A white woman, aged nineteen years, had a Cesarean section May 5, 1916, for eclampsia; the child was dead but the mother recovered, with a slight infection of the abdominal incision. The second pregnancy was normal in every way, the last menstruation having been the end of August, 1917; the patient went into labor and was sent to the hospital, where she stated that she had but a few typical labor pains, when these were followed by severe and constant pain over the entire abdomen, with rigidity of the abdominal wall. This persisted for three days, with fever and slight increased pulse. At about the fourth day the patient felt better and remained in the hospital awaiting active labor. No fetal heart sounds were heard after the abdominal pain, nor did the patient perceive fetal movements. About six weeks after the expected time of confinement the patient was examined, when the abdomen was enlarged to the size of a full-term pregnancy. The walls were so rigid that the fetus could not be palpated; there were no heart sounds. On vaginal examination no presenting part could be felt. The cervix was closed and firm, not resembling that of pregnancy. But one diagnosis seemed possible in the case, rupture of the uterus through the scar, with escape of the fetus into the abdominal cavity. At operation a thick spongy tissue was found just above the umbilicus, which proved to be a placenta. The amniotic sac was opened just above the placental area and about 2 quarts of amniotic fluid escaped. A large partly-macerated fetus was found lying obliquely in the abdominal cavity, the head above and to the right under the diaphragm, the extremities extending downward to the left. The amniotic sac was intact except where it had been incised on opening of the abdomen. After rupture of the uterus it had undergone involution, being about the size one would expect six weeks after labor. Through the line of the old incision the uterus had split asunder, extending from the fundus to about the level of the internal os. The placenta had been turned out through this opening, partly reimplanting itself later on the anterior parietal peritoneum. Both Fallopian tubes were covered with light adhesions and the right ovary was cystic, about the size of a small hen's egg. A subtotal hysterectomy was performed, the left ovary, which was normal, being saved. On removing the body of the uterus, with the tube, placenta, umbilical cord and fetus, a very large cavity was left. The inside of this was lined by tightly adherent amniotic membrane, which was removed where this was possible. The large cavity was treated by

placing several good-sized cigarette drains in various portions, bringing them out through the abdominal incision. The wound was closed in tiers, reinforced by interrupted silkworm sutures. The recovery from the operation was uneventful, the patient being discharged from the hospital three weeks after its performance. It was interesting to note in this case that although the uterus was ruptured there was no internal hemorrhage or shock. This has been seen by other observers. It is possible that the pressure of the child's head through the rent may have something to do with the prevention of the hemorrhage. There were no signs of old or recent hemorrhage, nor was there to any appreciable degree shock at the occurrence of the rupture. The occurrence of infection of the abdominal incision with fever for several days after Cesarean section in 1916 is very significant, and according to our knowledge of the causes of rupture of the scar this gives ample explanation for its occurrence in this case; the invasion of the uterine scar by decidual elements is thought by some to be an important factor.

Delivery by Abdominal Section.—Davis (*Am. Jour. Obst.*, May, 1918, reviews the conditions which are today admitted to be valid indications for delivery by abdominal section. He states that at present delivery through the vagina is limited to those cases in which a living child can thus safely be born with minimum injury to the mother. Great disproportion between mother and child with living child, accidental separation of the normal placenta, rupture of the uterus, ectopic gestation, a history of previous labor, with unusual difficulty with fetal mortality and maternal morbidity, and the presence of foreign growths making vaginal delivery impossible, give a clear indication for delivery by abdominal section. Placenta previa and prolapsus of the cord in primiparous patients, with partly dilated cervix and cases of eclampsia, where the birth canal is undilated and unyielding, are said by him to be valid reasons for delivery by section. The advantage of elective section at a time and under circumstances most favorable to patient and physician is set forth. The advantage of the classic section and the fact that it enables the operator to close the uterus most efficiently, thereby preventing subsequent rupture of the scar, are stated. Cesarean section for a peritoneal fistula is stated to give good results in the hands of those skilled in its employment, but it is not yet practised by the majority of American obstetricians. Should the indication be present to sterilize the patient the advantages of hysterectomy, with the removal of the tubes and ovaries and often the appendix, are considered sufficiently great to commend this operation. When delivery must be performed in septic cases the rule should be observed that the uterus should be extirpated or that the uterine stump should be left outside the peritoneal cavity. Delivery by abdominal section is undoubtedly the safest method of birth for the infant. The statement is made that the operation is not unnecessarily performed, and to illustrate this the records of 51 hospitals in one city are cited. In these in one year there were 78,905 operations described as surgical, 6498 operations called gynecological and 862 under miscellaneous headings (operations of the nose, throat, eye and ear), giving a total of 86,255 operations. During the same year in these hospitals there were performed 114 deliveries by

abdominal section. This would scarcely indicate that delivery by abdominal section is too frequently performed. The writer states that up to the time of writing his cases of delivery by abdominal section which were uninfected and in fairly good condition at the time of operation numbered 194, with a maternal mortality-rate of 1 per cent., and cases infected and in bad condition when delivered numbered 66, with a maternal mortality-rate of 30 per cent. The general mortality-rate was approximately 8 per cent., which compares favorably with other major surgical operations performed upon a similar number of cases varying in all degrees of preparation, absence of preparation and complicated and uncomplicated conditions.

Can the Frequency of Some Obstetrical Operations be Diminished?—VOORHEES (*Am. Jour. Obst.*, June, 1918) reviews the conditions pertaining in obstetric practice some years ago and draws attention to the fact that the high application of forceps and version are considered operations of very uncertain result and avoided if possible; craniotomy is rarely performed. Eclampsia has become much less frequent that formerly. The number of patients delivered in the hospital is greatly increased and there are more physicians who are specialists in obstetrics and there has been a general improvement in obstetric education. He believes, however, that there is still much indifference, ignorance and bungling work among the rank and file of the medical profession who practice obstetrics, and even obstetricians are guilty of mistakes and errors. One of the crying needs is for more faithful attention to pregnant patients to prevent toxemia; urine examinations should be frequently made and thoroughly done and a careful physical survey of the patient should be thoroughly conducted. A nitrogen partition in the urine should be made whenever indicated. If traces of albumin are found, a daily examination should be made. While it is true that acute fulminant toxemia may suddenly destroy a pregnant patient, most cases have premonitory symptoms, which call attention to the necessity for treatment, and if the patient does not respond to such treatment pregnancy must be interrupted. The writer states that in his private practice he has had but one case of eclampsia; before labor this patient did not obey directions, nor were specimens sent regularly. To illustrate the fact that eclampsia is becoming less he quotes the statistics of the Sloan Hospital; these show that from January 1, 1901, to December 31, 1905, inclusive, there were 113 cases of eclampsia in 7145 deliveries, or 1.5 per cent. From January 1, 1911, to December 31, 1915, there were 74 cases of eclampsia in 9224 deliveries, or 0.8 per cent. These statistics would indicate that more patients consult their physicians early in pregnancy and that the patients have better care. He calls attention to the value of correcting by external manipulations abnormal presentations. In the first 200 cases which the writer delivered there were ten breech presentations, while in the last 200 cases there were but six deliveries with that presentation. The writer admits that it may be impossible to change a breech to a head presentation in a primipara where the fetal legs are extended and this is especially difficult if there is a scanty amount of amniotic liquid. It is also possible in many cases to change a brow or face presentation to a vertex. In

all cases where there has been the production, in former pregnancies, of an unusually large child, measures should be taken to limit the development of the fetus in any subsequent pregnancies. This may be done conveniently by limiting the amount of carbohydrates which the woman takes after the sixth month. He calls attention to a case in which the patient had borne a first child successfully; in subsequent pregnancies there was great difficulty because the shoulders were largely developed and could only be delivered by extreme traction resulting in the loss of the child. In the third confinement a very strict diet was followed, with the result that a well-developed and nourished child was born spontaneously. In another case the induction of labor completed the care during pregnancy. To limit the over-development of a child he believes long walks during pregnancy are exceedingly valuable and also the wearing of a carefully-fitted corset. He draws attention to the success of Cesarean section in contracted pelvis; a very careful measurement of the pelvis will show that in the essential diameters there is considerable room; where however there is evident disproportion of a marked nature, then Cesarean section, often elective, gives good results. Regarding pituitrin, the conditions present for its safe employment are as follows: The cervix must be completely dilated and effaced and the membranes ruptured, the presentation normal and there must be proper relation between the fetal head and the maternal pelvis throughout. The writer has little confidence in the so-called "twilight sleep" method, but has found that nitrous oxide and oxygen are sometimes beneficial; if used too long and too frequently there is a distinct tendency to postpartum hemorrhage. The writer has faith in the efficacy of quinin and castor oil to bring on labor and in the action of a dilating bag introduced one or two weeks before full term. The statistics of the Sloan Hospital show that the use of forceps and the induction of labor are less frequently employed than formerly, but there seems to be an increase in the high forceps operation, which the writer says is surprising. Craniotomy is much less frequent; symphysiotomy and pubiotomy have been practically abandoned. Cesarean section has become much more common. He states the case of a primipara, aged thirty-six years, from whom had been removed the appendix and gall-stones. There was more or less abdominal pain and discomfort during pregnancy and the patient stated that she could not walk. Pelvic measurements were normal; the child was in breech presentation; this was changed to a vertex. An attempt to bring on labor by castor oil and quinin was made, but this failed; when labor developed it was delayed by an unusually firm cervix and a bag was introduced and later high forceps operation was performed. The child died as a result of pressure. The cervix was considerably torn and the mother made a tedious recovery complicated by phlebitis. The writer also states the case of a woman, aged thirty-eight years, in whom the fetus died from some unknown cause during pregnancy and after giving birth to several children; she lost several pregnancies by abortion and death of the fetus. This produced a condition of mental depression. Her last conception occurred when she was forty-four years old and the patient was carried on to within three weeks of term, when an elective section was done which resulted successfully. In this case the Wassermann reaction was always negative and no definite cause could be found for the death of

several of the children during pregnancy. The indication is that Cesarean section is frequently performed, and when the operation is chosen with good judgment the results are exceedingly good. It must, however, be remembered that in each case an operation is to be avoided rather than chosen and that very often ordinary measures, patiently and skillfully applied, are successful. It seems to the reviewer that while many obstetric operations are less frequently performed, there is a special need for skill and knowledge in obstetrics and for the exercise of good judgment. The success of Cesarean section impels many physicians and surgeons to undertake it who have not had experience to choose it wisely nor training to perform it properly. Good judgment is required to know upon what indication to induce labor, and no greater mistake can be made than the indiscriminate induction of labor. The management of pregnancy is most important as regards the labor which awaits the patient, and much can be done in this way to obviate dangerous and difficult procedures. The most hopeful sign in obstetric work is the fact that obstetrics is recognized as an important and distinct specialty for which special and thorough training is necessary, and which embraces a wide and important field in pathology and operative surgery. While certain operations may be less frequent, the demand for skill, experience and judgment is greater than ever before.

Sensitized Vaccines in the Prophylaxis and Treatment of Infections.—CECIL has contributed an extremely interesting paper upon this subject, giving a table of cases and the totals of his observations. His experience includes 20 cases in which sensitized typhoid vaccine was employed, 16 cases in which a sensitized gonococcus vaccine was used, 5 in which a sensitized streptococcus vaccine was employed and 1 case in which he employed sensitized Staphylococcus aureus; 4 cases of tuberculous adenitis and in 1 case of Pott's disease he used sensitized tuberculin. He finds that a vaccine sensitized with a homologous serum produces less disturbance when injected subcutaneously than does non-sensitized vaccine. In his series of 47 cases in typhoid it was found that the sensitized vaccine gave less reaction than the ordinary typhoid vaccine; as this may indicate that its protective power is less, it would not be advisable to substitute it at present for the ordinary vaccine. So far as the results obtained were concerned the sensitized vaccines gave no better effect that the ordinary vaccine. There were a few cases of recovery after treatment where ordinary vaccines had failed, but this may have been because a larger dose was used, which was made possible by the lessened disturbance produced by the sensitized vaccine. The chief objection to their use lies in the increased labor and time required in their production, and it would seem advisable to limit their use to those infections in which there is unusual sensitiveness to the ordinary vaccine or in which the ordinary vaccine had failed. While the writer does not mention puerperal septic infection, his cases include two patients suffering from gonorrheal vaginitis and one case of gonorrheal urethritis during the pregnant condition.

GYNECOLOGY

UNDER THE CHARGE OF

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Estimate of Radium Therapy in Uterine Cancer.—STONE (*Am. Jour. Obst.*, 1918, lxxvii, 390) has recently made a report on the estimated value of radium therapy in uterine cancer, based on a study of 400 cases treated at the Memorial Hospital in New York, 80 additional cases being under observation at the time of the report. Radium, they have found, is an agent more peculiarly suitable for the arrest of the progress of the disease than any other method that has been hitherto employed, being more effective in primary lesions than in recurrences. New patients are kept in the hospital three, four or more days in order that the medical records, physical examinations and laboratory tests may be made and sufficient time allowed to recover from the nausea and slight malaise which the application of radium may cause. For purposes of classification the cases are divided into (1) extremely advanced, (2) advanced, (3) borderline and (4) early. Extremely advanced lesions include those in which all the pelvic structures appear to be palpably involved, forming either bulky tumors in the upper part of the pelvis, and often extending far down into the septa between the vagina and rectum or bladder, or a large dugout, ulcerating crater surrounded by a mere shell of tumor tissue closely adjacent to the rectal and bladder walls. Stone feels that any interference with the nutrition of a tumor is an important factor in the result of radium therapy of tumors. A bulky and necrotic tumor never shows any improvement, and in lesions with an ulcerating crater, radium may cause the premature production of rectal and vesical fistulæ. In a few extremely advanced cases, however, if the nutrition of the tissues appears good, the application of a large amount of heavily screened radium, applied in a pack at some distance from the normal tissues overlying the tumor, will often afford considerable relief from pain. It is in advanced cases, where the parametrial tissues are definitely infiltrated, but where there is a palpable limitation of the tumor process, that radium is effective in arresting the process—relieving pain, stopping hemorrhage and discharge and restoring the general health—the adenocarcinomatous type being more susceptible to the action of radium than the infiltrating epithelioma. The changes produced by an effective dose of radium take place slowly, the tissues becoming edematous and softer by the end of the first week, the discharges sometimes being temporarily increased. By the third week the extra-uterine lesion is less well defined, the pain and discharge gradually diminish, until within two months little, if any, tumor tissue may be felt, leaving finally in many cases only an atrophic uterus fixed in tissue which is indistinguishable from fibrous connective tissue. In some cases a certain amount of tumor tissue may remain, though there is improvement in general health. How long is treatment to be continued in such cases? Under

further application of radium the lesion may improve, but a small ulcerating surface of the cervical mucosa may persist, due to poor nutrition in the surrounding zone of tissue, the age of the patient or overdosage at the first treatment. Radium will convert the borderline lesions, or those in which the growth is largely limited to the uterine wall, into operable lesions, and without surgery it will effect a disappearance of the gross evidences of the disease and restore health in a large number of such lesions more effectively than surgery alone has hitherto been able to do. Early lesions, either of the cervix or body, are rare. However, on the basis of experimental and clinical evidence the application of radium prior to hysterectomy in these early lesions would seem a justifiable mode of procedure. Prophylactic radium therapy after operation is important. It is possible that a number of low-power emanation tubes wrapped in the gauze drainage of the vaginal wound at the time of operation may prove an efficient means.

Biological and Clinical Evidence of the Therapeutic Value of Radium and Roentgen Rays in Cancer.—Last year Levin and Joseph reported the results of their investigations on the effect of radium and roentgen rays on cancer cells, by which they showed that radium may deeply impair the proliferating power and consequently the clinical malignancy of cancer cells without producing any change in the morphological appearance of the tumor. The first effect of the rays on a malignant tumor is the inhibition of the proliferating power, in sterilization, as it were, of the cancer cells, the degeneration and destruction of the cancer cells and the formation of the sclerotic connective tissue taking place subsequently under the influence of the rays. In a further recent series of investigations by Levin and Levine (*Ann. Surg.*, 1918, lxvii, 442) in the Department of Cancer Research at the Montefiore Hospital the above theories were further corroborated. The morphological appearance of radiated tumor tissue is not an absolute criterion of the therapeutic effect produced by the action of the rays on the tumor. While complete destruction of the tumor cells presents the most perfect result of radiotherapy, nevertheless negative morphological findings do not preclude the possibility that the tumor was influenced by the rays. In a series of twenty cases of carcinoma of the rectum which is being prepared for publication *in extenso* by the senior author, the following observation was made: In the cases in which an attempt at a radical operation was made the condition recurred with greater rapidity and malignancy than in those cases in which there was no operation done and only radium and roentgen-ray treatment given or an exploratory operation performed followed by radiations. Similar observations could be made by any surgeon with a large cancer material. Thus pre- and postoperative radiations of cancer as a method of inhibiting the proliferating power and the consequent clinical malignancy of the tumor cells is of undoubted value and presents no danger.

Treatment of Fibroid Tumors of the Uterus with Radium.—For the past five years Kelly (*Jour. Med. Soc., New Jersey*, 1918, xv, 145) has been treating fibroid tumors of the uterus with radium, having had altogether 211 cases under treatment, and he has found that all uncomplicated fibroids of whatever size are favorably influenced by

their treatment, which stops hemorrhage, together with menses, the latter either temporarily or permanently, and either causes the tumor to disappear completely or to shrink to very small dimensions. Before beginning radiation he makes sure that the case is one of uncomplicated fibroid tumor, excluding malignancy by curettage and histological examination and appendicitis, cholelithiasis and inflammatory conditions of the tubes and ovaries by careful examination. Of the 211 cases treated with radium at the present time 87 are cured, the tumors having either entirely disappeared or been so reduced as to be insignificant; 14 are so well that, in spite of repeated requests, they have failed to report for examination; in 62 instances the tumors have diminished in size. The last group is not static; it is composed largely of recently treated cases (less than two years), in which the radium has not had time to produce its full effect. The members of this group are constantly augmenting the first group. In addition to these 2 complicated cases are reported unimproved; 8 were operated on after radiation; 2 died of causes unconnected with the treatment; 12 have sent no report; 14 are too early for results and 10 did not complete treatment. Of the 2 cases reported unimproved 1 was complicated by gall-stones and operation advised, but refused; in the other a huge tumor choked the pelvis so completely that abdominal radiation had to be employed. Of the 8 cases operated on after radiation, in 3 cases the fibroid condition was complicated by ovarian cysts, in 2 bleeding was not controlled by a single radiation and, the patients desiring it, an operation was done; in 3 cases there was insufficient reduction of the tumor mass, a calcified uterus being found in one case. The technic as outlined by the author consists in the application of 300 to 500 millecuries of the emanation, covered with a rubber cot, on the end of a uterine sound within the uterus for about three hours. This may be repeated in a few months or an abdominal treatment may be given. For the latter form of treatment one or more grams of filtered radium are used. The package should be placed on the abdomen and shifted about for several hours, giving the skin a minimum and the tumor a maximum radiation. Immediately after treatment there may be nausea for twenty-four hours, some abdominal tenderness and possibly a leucorrheal discharge for several weeks. A second or third treatment is frequently required to bring about amenorrhea. In younger patients a mild treatment is given so that bleeding may be controlled, but menstruation continued. On the basis of his five years' experience the author feels that radium is the treatment of choice in uncomplicated fibroid tumors of the uterus.

Radium in Gynecology.—The great value of radium in fibroid tumors of the uterus is further borne out by the experience of WATKINS (*Surg. Clin. of Chicago*, 1918, No. 1, ii, 89). His patient, a woman, aged forty years, suffered from multiple fibroid tumors which made the uterus the size of a three months' pregnancy. Fifty milligrams of radium with 1 mm. brass screening covered by rubber were inserted into the uterine cavity. Three months later the uterus was normal in size, no tumor could be palpated and the patient had skipped the last two periods. In case of chronic metritis, Watkins's results were equally encouraging, the hyperplastic uterus becoming normal in size, two periods following radium insertion, then a cessation for eight months

followed by regular menstruation. In a case of submucous uterine fibroid with cancer, the results were not so good, rectal and vesical symptoms following the application of radium probably because of insufficient screening. During the next three months the deep growth increased rapidly in size, though there was no recurrence of bleeding, discharge or odor, and the superficial wound healed. In a case of extensive inoperable cancer of the body of the uterus there could be no hope of cure, but three administrations of radium were of great palliative benefit, being followed by a marked diminution in pain, a cessation of all offensive discharge and absence of bleeding up to the time of death. He therefore believes that the value of radium as a palliative measure in these very grave cases cannot be overemphasized.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Acute Respiratory Diseases Among Troops, with Special Reference to Empyema.—Beals, Zimmerman and Marlow (*Jour. Infect. Dis.*, 1918, xxiii, 475) report their findings from a study of acute respiratory diseases occurring among troops from September 25, 1917, to June 1, 1918. Out of a total of 9691 admissions to a base hospital, 4443 were cases of acute respiratory infections. The cases occurred in waves with the greatest severity at the crest of each wave. During a period of three months there were 333 cases of measles (including rubella), only 3 cases having complications, otitis media in each instance. Later, when respiratory infections developed, there were not only many cases of pneumonia and empyema, but the cases of measles, though not greatly increased in number, showed severe complications of a respiratory infection, usually streptococcic in origin. Empyema, pneumonia, tonsillitis, otitis media and severe bronchitis were found accompanying measles. The mortality was high, 61.5 per cent., in cases of empyema following measles. When empyema complicated pneumonia the mortality was 38.2 per cent., and in the 22 cases of primary empyema death occurred in 5 cases, or 22.7 per cent. The authors note four distinct types of empyema—fibrinous, serofibrinous, serofibrinopurulent and purulent. The authors found that for a variable period of about a week there was a serofibrinopurulent exudate, and at autopsy there was often found a serofibrinopurulent exudate in one pleural cavity and a fibrinous or serofibrinous in the other. In the majority of cases a streptococcus, usually hemolytic, was the causative agent. The clinical manifestations include rapid and profound toxemia, the rapid formation of, in most cases, a large amount of pleural exudate and a tendency to pocket formation by old and new adhesions in atypical locations. The most marked autopsy findings were the presence of wide-

spread lesions involving serous membranes, severe bronchitis, in the majority of cases, and a type of bronchopneumonia often closely resembling a lobar process. The authors note the importance of an early recognition of empyema, especially in the acute fulminant type of cases. Diagnosis, they state, depends on close attention to clinical progress and proper interpretation of the physical signs. Control of such epidemics depends on sanitation of the barracks, with adequate space and proper separation, especially of those even slightly affected with respiratory diseases.

Experimental Chemical Pneumonia.—Considerable interest surrounds the question of the nature of the pulmonary reaction under different conditions of irritation. WOLLSTEIN and MELTZER (*Jour. Exper. Med.*, 1918, xxviii, 547 and 551) were led to carry on a series of observations upon the reaction developing within the lung when different chemical substances in solution were introduced. Their attention was attracted to these pulmonary lesions during an investigation upon the treatment of lobar pneumonia by local application of chloramine-T to the infected lung. Animals were primarily infected with pneumococcus cultures by bronchial insufflation, and after two hours 5 c.c. per kilo weight of a 1 to 10,000 solution of the antiseptic was run into the bronchi. They found that this solution was injurious to the pulmonary tissue and appeared to intensify the pathological process. When using the antiseptic solution alone they were able to produce a bronchopneumonia, with marked congestion and edema. Leukocytes attended the pulmonary reaction, but very little fibrin was present. At the end of twenty-four hours some resolution was beginning, and it was almost complete on the seventh day. Similar effects were obtained by the use of Dakin's solution. In another series of experiments the use of mercuric chloride in weak solution gave reactions differing somewhat from these, at times being associated with local thromboses. The lesions were hemorrhagic, but they found they were unattended by a true inflammation. Salt solution gave slight or negligible responses, as did also a solution of sodium sulphate. Magnesium salts are somewhat more irritating and caused moderate pulmonary lesions. The authors indicated that the use of magnesium salts is fraught with danger on account of the deep anesthesia and paralysis of respiration.

Studies of Bacteriemias in the Agonal Period.—There are several points of interest in a study of the bacterial flora of the body at the time of death. The occurrence of bacteria in the blood stream during the terminal stages of patients chronically ill serves as an index of the increasing susceptibility, or better, of the loss of the natural resistance against infection. It is often stated, but less often proved, that severe debilitating diseases increase the non-specific susceptibility of the body. In the work of RICHEY and GOEHRING (*Jour. Med. Res.*, 1918, xxxviii, 421) they have studied several phases of this problem. They have demonstrated by taking blood cultures at the time of death that individuals who have been seriously ill over a considerable period of time not uncommonly have a bacteriemia. These blood-stream infections are absent in individuals who have suffered an acute accidental death. The organisms most prone to invade the body are the streptococci and pneumococci. The studies were made on a series of 206 blood cultures

taken not later than ten minutes after death. Positive blood cultures were obtained 76 times, from which 87 organisms were isolated. The pneumococcus was present in 32 cases while the Streptococcus pyogenes was present 16 times. Inasmuch as the majority of the cases in which the pneumococcus was isolated were lobar pneumonia, the invasion of the blood stream by the microörganisms took place before the agonal period. They have shown, however, that the bacterial flora of the blood stream may change so that a new infection is introduced upon a previous one during the agonal period. The technic carried out in these studies gave more accurate results than those usually obtained from heart cultures at autopsy.

Acid Production by Bacteria.—A number of methods are available to us for the demonstration and determination of the acids produced by the growth of bacteria in carbohydrate media. The majority of methods in use in bacteriology simply indicate the ability of particular organisms to produce acid from a certain carbohydrate. A few other methods which are but rarely used are for the purpose of determining the quantity of acid which is produced after a given time of cultivation. There has always been a certain technical difficulty of determining in a given culture the amount of acid present from day to day and the speed with which the sugar in the medium has been used up. FISCHER (*Jour. Exper. Med.*, 1918, xxviii, 529) has devised an instrument whereby he may graphically record the quantity of acid during the entire period of growth. The author makes use of the acid resulting in bacterial growth to act upon calcium carbonate, and by collecting the gas in a delicately balanced cylinder he obtains a record of the movements of this cylinder upon a revolving drum. The apparatus as devised appears rather cumbersome, although the results are quite striking. In his preliminary study he has tested some of the coli group. By means of the instrument he is able to record the time when acid production begins and the speed with which it then takes place. He is also able to determine the time when the carbohydrate is entirely used up. The onset of acid production varies with the concentration of the sugar and the total quantity of gas liberated by the action of the acid on the calcium carbonate is in direct proportion to the carbohydrate content of the medium. The graphic curves which are recorded by the instrument are interesting, particularly when organisms with a known curve are cultured with other bacteria. Under these circumstances new curves which are at times more difficult of interpretation are obtained.

Observations on the Presence of Meningococcus in the Blood.—Within the last years a number of reports have appeared concerning the findings of the meningococcus in the blood stream. These reports dealt with cases of meningitis in which the blood infection was only an incident in the disease. A suggestion, however, was brought forward that the organisms gain entrance to the blood stream prior to their localization upon the meninges. It was the desire of MAXCY (*Jour. Infect. Dis.*, 1918, xxiii, 470) to demonstrate such a preliminary blood-stream infection in cases subsequently developing meningitis as well as in others in whom the blood-stream infection was transient and of an "abortive type," never leading to a meningral infection. For this purpose they studied meningitis "suspects" presenting minor clinical

manifestations. Negative results were obtained in the blood cultures from 27 such cases. However, during the course of the investigations 2 cases of epidemic meningitis were encountered illustrating the relative unimportance of the blood-stream invasion in one and the apparent great importance in the other. In the first instance the meningococcus was isolated within twenty-four hours of the clinical manifestations. In the second case the meningeal manifestations were not apparent until the fifth day of the disease. The meningeal infection yielded to intraspinal serum treatment at the end of three weeks. At this time the meningococcus was isolated from the blood stream and was reisolated on two successive occasions, covering a further period of two and a half weeks. No focus of distribution for the meningococcus could be demonstrated in the nose.

Relationship of the Leukocyte Count and Bone-marrow Changes in Acute Lobar Pneumonia.—In acute lobar pneumonia the clinician pays much attention to the leukocyte count for the purpose of following each case and for indicating the probable outcome. It is well recognized that the number of leukocytes in the circulating blood varies within wide limits during this acute respiratory disease. The low count is often taken as a grave omen in the outcome of the case. On the other hand, fatal cases may occasionally show a very high count. SAMMUELS and LAMBERT (*Jour. Infect. Dis.*, 1918, xxiii, 443) have studied 17 cases of acute lobar pneumonia, with the object of determining the reason for the marked variation in the number of circulating leukocytes. Various authors had previously suggested reasons for the leukopenia, claiming that this state arises from a lack of response on the part of the bone marrow in producing leukocytes. The authors studied the bone marrow of the femur in all of their cases. They were able to compare the leukocyte count during life with the bone-marrow findings. In a few cases a parallelism between the leukocyte count and the character of the bone-marrow was found: that is, when a persistently low number of leukocytes were present in the blood the bone-marrow was aplastic, and when the leukocyte count was high the marrow was markedly hyperplastic. On the other hand, in the majority of cases no such agreement was found. In several cases a striking lack of harmony between the bone-marrow and the blood changes existed. In one case showing marked hyperplasia of the bone-marrow there was a relatively low count, while in another individual, with a leukocyte count from 19,000 to 27,000, the marrow was aplastic. To explain the latter state they indicate that the origin of the leukocytes must have been in the flat bones or in tissues other than bone-marrow. They are at a loss to explain a hyperplasia of the marrow associated with a low leukocyte count. They do not believe that this results from a rapid drainage of cells out of the circulation.

Experimental Carcinomata of Animals and Their Relation to True Malignant Tumors.—Within recent years several investigations on the experimental production of malignant growths in animals have been published, and these reports BULLOCK and ROHDENBURG (*Jour. Cancer Res.*, 1918, iii, 227) subject to a critical analysis, in which especially the claims of Fischer, Fibiger, Stahr and Yamagiwa and Ichikawa are discussed. Bullock and Rohdenburg, experimenting on a large num-

ber of animals, produced by various forms of chronic irritation epithelial growths similar to those described by the above-mentioned authors, in order to ascertain whether these lesions might not be interpreted as hypergenerative processes rather than true carcinomata. The introduction into the stomach of the rat of celluloid balls covered with pins or bristle spines was followed by polypoid and papillary tumors, which simulated the gastric cancers which Fibiger produced by feeding these animals cockroaches. Microscopically these reactions were characterized in general by hypertrophy of the epithelium, with extensive production of keratin and a proliferation and downgrowth of epithelium toward the muscularis mucosa. Not infrequently ulcers and lesions in the glandular portions of the stomach suggesting cystadenomata resulted. When Scharlach R or pine tar was injected into the wall of the stomach or cotton wicks or rubber sponges impregnated with these substances were placed in the viscus, the formation of papillomatous tumors in the glandular portion and lesions resembling epitheliomata in the squamous region occurred in from seven to fifteen days. An attempt to duplicate the papillomatous tumors of the rat's tongue, described by Stahr, which arose after prolonged ingestion of oats, was made by inserting the fine hairs of bearded wheat or foxglove into the dorsum of the tongue. Ulceration about the hairs, with a considerable proliferation and hypertrophy of the lingual epithelium, resulted. Repeated injection of Scharlach R into the region of the papilla vallata gave rise to a metaplasia of the serous and mucous glands of that region, with the production of lesions simulating benign epithelial growths. Lesions indistinguishable morphologically from human epitheliomata were caused by repeated injections of Scharlach R in oil into the skin of the buttocks in rabbits. As a result of their experiments these authors conclude that a typical proliferation and invasive growth in the presence of an irritant form a doubtful criteria upon which to base a judgment of malignancy, and especially when these irritation tumors show no relation to the age of the animal and an absence of continued growth upon removal of the irritation or upon transplantation.

Importance of the Lymphocyte in Cancer Immunity.—Much interest has centered about the relation of the lymphocyte to the spontaneous or induced cancer of animals. Da Fanco was among the first to observe that receding tumors in cancer immune animals were constantly surrounded by a zone of lymphocytes, which he assumed had an important bearing on cancer immunity. Others have confirmed these observations. Later it was reported that mice having a resistance to cancer implantation showed a higher number of circulating lymphocytes than in the susceptible ones. These assumptions concerning the relation of lymphocytes to cancer immunity have been put to experimental tests. Inconclusive results have been obtained, inasmuch as various experimenters were unable to agree with the results obtained by others. SITTENFIELD (*Jour. Med. Res.*, 1918, xxxviii, 465) induced a high lymphocyte count in the circulating blood by repeated injections of pilocarpin. These rats were then inoculated with a transplantable rat cancer and the results compared with controls. A passive lymphocytosis was also induced in other animals by stimulating doses of roentgen rays and transferring the collected lymphocytes into a normal animal. These second animals were also inoculated with a rat cancer.

In none of these was the author able to observe any definite immunity in the animals with the hyperlymphocytosis. In another series of experiments the author made use of animals refractile to cancer implantation, reducing their lymphocytes by intensive roentgen-ray treatment. Their immunity to the cancer inoculation was then tested in the hope that a greater susceptibility could be demonstrated. In this he was disappointed. These results are contrary to those reported by Murphy and Morton. The author continued his experiments by a new procedure. In these the author excised the main tumor mass from rats which had been inoculated with tumor. These animals were then given stimulating doses of roentgen rays to increase the lymphocytes and then were reinoculated with their own tumor. He found that these animals did not develop any immunity to their own tumor even though a lymphocytosis was obtained before reinoculation. When the tumor was incompletely excised the tumor grew at the site of the second inoculation and recurred in 48 per cent. at the site of excision. The author concludes that the degree of lymphocytosis had very little to do with immunity to the tumor used in these experiments. In repeating the work of Murphy and Morton the author was unable to confirm the findings relating to the importance of the induced lymphocytosis as a factor in tumor immunity.

Spirillosis.—HARTMAN and LACY (*Jour. Infect. Dis.*, 1918, xxiii, 449) report the bacteriological findings in the case of a young Italian having clinical manifestations suggesting typhoid fever. The patient suffered from a chronic cough and indefinite gastro-intestinal discomfort. There was some diarrhea. His temperature was of an intermittent character and he had general glandular enlargement, with splenomegaly. All tests for a typhoid infection were negative. He had a low red-cell count which continued to be depressed during the period of observation. During life and after death a peculiar organism was isolated from the blood stream. The microörganism was very pleomorphic, developing into long threads and spirals, but often showing short and coccoid forms. The authors were unable to classify the organism.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Physiological Effects of Siliceous Dust on the Miners of the Joplin District.—LANZA (*Bulletin No.* 132, *Department of the Interior, Bureau of Mines*) states that there is much pulmonary disease due to rock dust

among the miners of the Joplin district, affecting probably as high as 30 per cent. of sheet ground miners. The amelioration of dust-producing conditions is progressing at a reasonable rate. Living conditions are generally poor, and often needlessly bad. Although miners' consumption and tuberculosis of the lungs are entirely different diseases, as regards the public health, no distinction should be made as to precautions against spread of infection. The prevention of the spread of tuberculous infection, especially to children in the homes of consumptives, is of paramount importance. The combination of hard work with a short dinner period is injurious and unnecessary.

Report on Attempts to Cultivate the Virus of Epidemic Poliomyelitis.—WAYSON (*Hygienic Laboratory Bulletin No.* 111, p. 35) cultivated numerous diplococci and streptococci from the spinal cords and brains of human and monkey subjects which showed, clinically and histologically, the findings in acute epidemic poliomyelitis. None of the organisms cultivated reacted in the small laboratory animals nor in the monkeys with clinical or histological evidence of the disease. The attempt to produce Noguchi's and Rosenow's results were negative, although involving approximately 700 primary cultures and 300 animal tests. Wayson states that in view of the not infrequent reports in the literature for many years of myelitis and poliomyelitis experimentally produced by the injection of streptococci isolated from various sources it is remarkable that none were found among his experiments. The negative findings in attempts to reproduce the results of Noguchi and Rosenow, though carrying out their technic as guided by their writings, would suggest that the virus used did not contain organisms similar to those found by these investigators or that the organisms were of unusual sensitivity, and were lost by imperceptibly slight modifications made of the technic. Diplococci and streptococci were found in several samples of ascitic fluid, when cultures were made under a lowered oxygen tension. Therefore the presence of such organisms in cultures, to which has been added raw ascitic fluid, should not be misinterpreted. The organisms are frequently present in small numbers and may require the development of several days' incubation before they become evident.

Color Blindness: Its Relation to Other Ocular Conditions and the Bearing on Public Health of Tests for Color-sense Acuity.—COLLINS (*Public Health Bulletin No.* 92) states that color blindness is best detected by testing with colored lights of known spectral composition. It is of great importance to divide the color blind into the dangerously color blind and the harmlessly color blind. This may be done satisfactorily and expeditiously with the Eldridge-Green lantern after gaining an understanding of the principles of the test employed. The Jennings test results in the rejection of a large percentage of subjects who should be accepted, especially among the more intelligent, but it possesses certain lines of examination where great accuracy and classification of color defects are not essential. It should not be used for testing sailors or trainmen. In every-day life among healthy individuals in America, color blindness (excluding the pentachromic) occurs in about 8.6 per cent. of men and 2.2 per cent. of women. Color blindness of a degree dangerous in occupations requiring recognition

of colored signal lights occurs in about 3.1 per cent. of men and in about 0.7 per cent. of women. Among refractive conditions of the eye, color blindness occurs least frequently in eyes apparently without demonstrable refractive error; it occurs most frequently in eyes showing mixed astigmatism.

Transmission of Poliomyelitis. —TAYLOR and AMOSS (*Jour. Exper. Med.*, November 1, 1917, p. 745) present evidence toward the solution of the problem of the mode of infection in poliomyelitis by means of secretions from the mouth and nose. This theory was first propounded by WICKMAN (*Beiträge zur Kenntnis der Heine-Medinschen Krankheit*, Berlin, 1907), whose clinical studies disseminated the view of the personal factor in the communication of the virus of poliomyelitis. The occurrence and epidemiological importance of the nonparalytic or abortive cases and of healthy carriers were also emphasized by Wickman. The credit, however, of first calling attention to nonparalytic cases in epidemic poliomyelitis belongs to an American sanitarian, CAVERLY, who recorded 6 cases among a total of 132 cases in the Rutland epidemic of 1894 (*Jour. Am. Med. Assn.*, 1896, xxvi, 1). FLEXNER and LEWIS, in 1910 (*Jour. Am. Med. Assn.*, 1910, liv, 1140), detected the virus in the nasopharyngeal mucous membrane of infected monkeys. KLING, PETTERSSON, and WERNSTEDT (*Com. Inst. Med. Etat. à Stockholm*, 1912, iii, 5) injected monkeys with buccal washings from so-called abortive cases and from healthy carriers, with, however, inconclusive results. ROSENAU, SHEPPARD and AMOSS (*Boston Med. and Surg. Jour.*, May 25, 1911, clxiv, 21, pp. 743–748) and others were unable to demonstrate the virus in the nasal and buccal secretions obtained from persons in various stages of convalescence. Recently, AMOSS and TAYLOR (*Jour. Exp. Med.*, 1917, xxv, 507) demonstrated that the nasopharyngeal secretions are able to neutralize an active poliomyelitis virus, which may account for the negative results. In 1913, FLEXNER, CLARK and FRASER (*Jour. Am. Med. Assn.*, 1913, lx, 201) demonstrated experimentally that the parents of E. A., neither of whom showed any symptoms of illness, and who evidently were not suffering from poliomyelitis, nevertheless harbored the virus of the disease in the nasopharynx. E. A. suffered with severe paralytic poliomyelitis, from which he subsequently improved. Hence, the existence of the healthy carrier was established experimentally. The next demonstration was supplied by KLING and PETTERSSON (*Deutsch. med. Wchnschr.*, 1914, xl, 320), who studied a family in which one or more healthy carriers of the active virus of poliomyelitis were demonstrated. In these two successful instances, mixed washings were employed for inoculation. TAYLOR and AMOSS studied a family consisting of the father, aged fifty-nine years; mother, aged forty-two years; Carey, aged sixteen years; sister, Hazel, aged thirteen years; two brothers, Everett, aged ten years, and Dwight, aged seven years. The two younger brothers slept in the same bed and in the same room with the elder brother, Carey. They found that only one child—the eldest boy, Carey—was exposed in a locality in which poliomyelitis was epidemic. The exposure took place on June 2. Immediately afterward he returned home, to a village in which no previous case of the disease was known, and mingled freely with his younger brother and sister.

The contacts may be considered to have been intimate in that the three male children slept in the same room, two of them in the same bed. The incubation period in Carey's case was nine or ten days, as he was taken ill on June 12. His brother Everett, six years younger, developed symptoms one day later and passed through what was probably a non-paralytic attack of poliomyelitis. He may be considered as having been infected by Carey some time during the incubation period and to have exhibited a shorter incubation than his brother. The youngest brother, Dwight, was also freely exposed to both older brothers, and exhibited symptoms passing into those indicative of poliomyelitis five or six days later than his brothers. Finally, Hazel, the sister, in age between the two older brothers, and possibly less freely exposed, developed symptoms and muscular weakness last of all, and about ten days after the eldest brother. The incubation periods of the cases therefore probably were ten days or less, and the order of the attacks was such as to indicate successive infection and not a common one. The second feature worthy of emphasis is the detection in this one family of two carriers of the poliomyelitic virus by the inoculation test. One (Everett) was discovered to be a carrier probably following a non-paralytic attack. In the instance of Hazel there is no doubt, first, that she was discovered to be a carrier, and second, that she developed typical poliomyelitis during the period of carriage. Incidentally the nasopharyngeal secretions of Hazel and Everett failed to neutralize the poliomyelitic virus. Taylor and Amoss, furthermore, state that if the view that the mode of infection in epidemic poliomyelitis is by way of the nasopharyngeal mucous membrane and is brought about or greatly facilitated through the operation of healthy carriers of the virus, we may well consider whether in the final analysis every case of the disease does not develop from a carrier. At first this may seem startling, and yet it merely means that after contamination of the nasopharynx with the virus an intervening period exists during which persistence, multiplication, and invasion of the virus take place. In not all contaminated persons does this process become complete; in some the virus may merely persist for a time, in others it may multiply in the nasopharynx (these constitute the healthy carriers of greater or less endurance), while in the exceptional few invasion also occurs. In the latter, symptoms arise, and such individuals compose the class of poliomyelitis cases. In brief, then, a family containing four children, all of whom showed in varying degrees organisms of poliomyelitis, is described. The source of infection and periods of incubation have been followed. Two of the children were proved by inoculation tests to carry the virus of poliomyelitis in the nasopharynx. Of these, one was detected to be a carrier after recovering from a non-paralytic attack of the disease and the other was discovered to be a carrier about five days before the initial symptoms, attended later by paralysis, appeared. The original case from which the three others took origin was fatal; the youngest child, after quite a severe onset, was treated with immune serum, and made a prompt and almost perfect recovery. The nasopharyngeal secretions of 2 of the cases, taken one month after the attack, proved incapable of neutralizing an active poliomyelitis virus. The proposition is presented that every case of poliomyelitis develops from a carrier of the microbic cause, or virus, of poliomyelitis.

Clinical and Epidemiological Studies on Epidemic Meningitis.—Robey, Saylor, Meleney, Ray and Landmann (*Jour. Infect. Dis.*, October, 1918) studied a group of 26 cases of epidemic meningitis which were admitted to the Base Hospital at Camp McClellan, Alabama, between September 27, 1917, and April 4, 1918. They found that the use of a good polyvalent antimeningococcus serum together with four types of monovalent serum for agglutination tests detects more accurately all types of meningococci, in routine work on a large scale, than does either polyvalent or monovalent serum used alone. Most of the meningococcus carriers in a company in which a case of meningitis occurs harbor an organism of the same type as that causing the case of meningitis. It is usually possible to find a chronic meningococcus carrier in a company in which a case of meningitis occurs. Three consecutive negative cultures taken at three-day intervals do not ensure permanent freedom of a carrier from the meningococcus. At least five negative cultures taken at three-day intervals should be required and the carrier cultured at intervals after release. The meningitis at Camp McClellan during the winter is considered to have been a series of sporadic cases, not an epidemic.

Diagnosis of Epidemic Meningitis and the Control of its Treatment by Rapid Bacteriologic and Serologic Methods.—Cohen and Fleming (*Jour. Infect. Dis.*, October, 1918) describe simple, rapid and accurate methods for the isolation and cultivation of the meningococcus as a result of their studies on the subject. They call attention to the fact that the meningococcus is a micro-aërophil. They measured the optimum reduction in oxygen tension for meningococcus cultures. They found that meningococci grow best in an atmosphere composed of approximately 10 per cent. CO_2 and 90 per cent. air. In 500 nasopharyngeal cultures 10.8 per cent. carriers were found by CO_2 and 1.4 per cent. by the usual method.

Comparison of Methods for the Examination of Water at Filtration Plants.—Norton (*Jour. Infect. Dis.*, October, 1918) compiled statistics concerning the methods of water examination in connection with 24 purification plants in this country and found that in no two instances were the methods exactly alike. He states that about two-thirds of the laboratories use gelatin as the medium for obtaining a total count at 20° C. The procedures with this medium are fairly consistent. About seven-eighths of the laboratories use an agar medium for counts at some temperature while 60 per cent. conform to a twenty-four-hour count at 37° C. The composition of the medium is as consistent as possible with ingredients from varying sources. Many differences are found in the methods for the detection of organisms of the type B. coli. About 60 per cent. of the laboratories use lactose broth and most of the remainder use lactose bile. In somewhat less than half of the instances the presumptive test only is made while the others use a great variety of confirmatory tests. No definite relation is maintained between gelatin and agar counts. In order to be comparable, data of water examinations must be collected under identical conditions. Since no uniformity in methods exists among the laboratories in this country, bacteriological data of water supplies and water purification processes are not amenable to critical comparisons.

Further Studies on Bacterium Abortus and Related Bacteria.—EVANS (*Jour. Infect. Dis.*, October, 1918) reports the results of her studies on methods designed to give the numbers as well as kinds of bacteria of the type of Bacterium abortus and related strains found in freshly drawn milk. Bacterium lipolyticus and other abortus-like bacteria were isolated from the milk of 10 to 24, or 41.7 per cent. of cows which had not aborted. The cows belonged to a herd in which there was an occasional abortion, but no general outbreak. The same kinds of bacteria were isolated from the milk of 100 per cent. of 12 cows which had aborted as a result of natural infection. Bacterium lipolyticus was cultivated from the milk of 66.6 per cent. of these cows and other abortus-like bacteria were cultivated from the milk of 50 per cent. of them. Typical virulent strains of Bacterium abortus could not be isolated from the milk of either of the above-mentioned groups. Typical Bacterium abortus was found to be present in very large numbers in the milk of 2 cows that had been repeatedly inoculated with a mixture of strains of that organism. It was found only once, in rather small numbers (450 per c.c.) in the milk of another cow which aborted after receiving one inoculation. The data indicate that virulent strains of Bacterium abortus are not eliminated continuously in large numbers in the milk of cows which have aborted even though the blood serum continues to react positively to the agglutination test. The author discusses the characteristics of Bacterium lipolyticus and other abortus-like bacteria and their relation to the typical Bacterium abortus; also the possibility that some of these strains may cause abortions in those cases in which the blood serum reacts negatively to Bacterium abortus antigen. The bacterial flora of the udders of a herd in which there existed an outbreak of abortions was found to be abnormal in the large numbers of udders which were infected with streptococci, and it was also abnormal in showing a general infection with a streptothrix. Abortus-like bacteria were found in 66.6 per cent. of the samples of milk. The abortus-like bacteria included 7 acid-producing strains which had never before been found.

Streptothrix (Nocardia) Infection of Cows' Udders.—EVANS (*Jour. Infect. Dis.*, October, 1918) studied the bacterial contamination of cows' milk as it comes from the udder. A streptothrix (nocardia) was isolated from 85.7 per cent. of the infected udders examined. Streptothrices are common saprophytic and parasitic organisms which occur in soil and water and are associated particularly with herbage. They are the cause of many diseases, and infection has in many cases been traced to herbage. Cattle are the most susceptible animals, and the most common diseases caused are lumpy jaw and pneumonia. In human beings the most common infections are about the mouth or in the neck, as the result of oral infection. The next common seat of apparent primary infection was the appendix, and next was pulmonary infection. In the tropics Madura foot is a common disease caused by a streptothrix. Evans states that any comment on the possible sanitary significance of large numbers of a streptothrix in milk would be mere conjecture. Animal inoculation would not give reliable information on this point, for numerous investigators who have studied the streptothrices agree that pathogenicity is not a reliable specific character. The finding

of streptothrices in milk merely adds a fourth organism to the three types of bacteria of a suspicious character already known to occur in milk freshly drawn from normal udders—the streptococci, the staphylococci and the rod-forms of the Bacterium abortus type. Thus the streptothrix may prove to be still another source of danger in the use of raw milk as food, and may furnish an additional reason for taking advantage of the safeguard afforded by pasteurization.

Prevailing Pandemic of Influenza.—KEEGAN (*Bulletin No.* 44, *Division of Sanitation, Bureau of Medicine and Surgery*, United States Navy Department) states that a rapidly spreading pandemic disease was first recognized at the United States Naval Hospital, Chelsea, Mass., August 28, 1918, the first patients coming from the receiving ship at Commonwealth Pier, Boston, Mass. It has been carried to this port from Europe, both by patients and by carriers. It promises to spread rapidly over the entire country, attacking 30 to 40 per cent. of the population and running an acute course of four to six weeks in each community. This disease is characteristic of the ordinary endemic influenza, but is more severe and much more contagious. It is caused by a specific virulent strain of the influenza bacillus, against which individuals of the younger generation have relatively no immunity. In 5 to 10 per cent. of the persons afflicted it develops into a massive and very fatal bronchopneumonia. This pneumonia is primarily caused by the influenza bacillus, this microörganism being recovered from 82.6 per cent. of the lungs at autopsy, in 31.6 per cent. of which it was found in pure culture. The pneumonia is frequently complicated by pneumococcus or streptococcus infection. The disease is characteristic of a sudden and severe toxemia, the influenza bacillus not being in the blood at any stage. The disease is not due to a filterable virus. This was determined by introducing the filtrate of nasal and throat washings from two typical cases into the anterior nares of nine volunteers, with negative results.

Rat and Poliomyelitis.—AMOSS and HASELBAUER (*Jour. Exp. Med.*, October 1, 1918, p. 429) state that their experiments bring out a remarkable similarity between the tests on the rat and those made by Amoss previously on the rabbit. Indeed, it appears that the rat is an even more unfavorable host for the virus of poliomyelitis than is the rabbit, since in the former animal an effective dose of the virus for the monkey was no longer detectable at the expiration of four days. This fact is hardly consistent with the theory that the rat constitutes a natural reservoir in nature of the virus. Rather the experiments would indicate that the rat's organism is wholly unadapted to its multiplication and survival. The central nervous organs and other viscera of six rats, collected in a district in Greater New York in which many cases of epidemic poliomyelitis occurred, have been proved incapable of inciting, on inoculation, experimental poliomyelitis in Macacus rhesus monkeys. The virus of poliomyelitis injected into the brain of white rats does not survive there as long as four days in a form or in amounts sufficient to cause infection when inoculated intracerebrally into monkeys. The failure of the virus injected into the brain of rats to incite infection in monkeys is not due to the quantity introduced, since at the expiration

of one and a half hours after the injection the excised inoculation site when injected into the monkey caused typical experimental poliomyelitis. It does not appear probable, therefore, that the rat acts in nature as the reservoir of the virus of poliomyelitis.

Further Study of Experimental Parotitis. — WOLLSTEIN (*Jour. Exper. Med.*, October 1, 1918, p. 377) describes a new series of inoculations into cats of the filtered sterile salivary secretions derived from cases of parotitis. They confirm the observations made by her in 1915–16 and extend them to include the epidemic parotitis occurring in our military forces. Incidentally, confirmatory evidence of the filterable nature of the causative agent of mumps has been obtained. It has been determined that the saliva of man and of inoculated cats, and the inoculated glands of the latter animals, contain the filterable, infective agent. The lesions present in the inoculated organs conform to those previously found. In addition the lymph glands adjacent to the salivary glands on the uninoculated side were sometimes found to be swollen and to exhibit microscopic lesions. Probably the involvement resulted from salivary and lymphatic infections. The "virus" of parotitis was detected most readily in the saliva during the first three days of the disease, less easily on the sixth day and not at all on the ninth day. It was detected also in the blood of patients showing marked constitutional symptoms and in the saliva of a case of recurrent mumps at the periods of enlargement of the parotid glands, but not two weeks after the swelling had subsided. It was not detected in the cerebrospinal fluid.

Spirocheta Hebdomadis, the Causative Agent of Seven-day Fever.— IDO, ITO and WANI (*Jour. Exp. Med.*, October, 1918, p. 435) describe a new species of spirochete, which they call Spirocheta hebdomadis, as the specific etiological agent of seven-day fever, a disease prevailing in the autumn in Fukuoka and other parts of Japan. This spirochete is distinguishable from Spirocheta icterohemorrhagiæ, to which it presents certain similarities. Young guinea-pigs are susceptible to inoculation with the blood of patients and to pure cultures of the spirochete and those developing infection exhibit definite symptoms suggestive of those of seven-day fever in man. The blood serum of convalescents from seven-day fever contains specific immune bodies acting spirochetolytically and spirocheticidally against the specific spirochetes, but not against Spirocheta icterohemorrhagiæ. The field mouse (Microtus montebelli) is the normal host of the spirochetes, which have been detected in the kidneys and urine of 3.3 per cent. of the animals examined. The endemic area of prevalence of seven-day fever corresponds with the region in which field mice abound.

Report on Antimeningitis Vaccination and Observations on Agglutinins in the Blood of Chronic Meningococcus Carriers.—GATES (*Jour. Exper. Med.*, October, 1918, p. 449) states that a meningococcus vaccine suspended in salt solution has been given subcutaneously as a prophylactic to about 3700 volunteers in three injections of 2000 million, 4000 million and 4000 to 8000 million cocci at weekly intervals. These doses rarely caused more than the mildest local and general reactions.

Exceptionally a more severe reaction emphasized the presence of an unusual individual susceptibility to the vaccine. In such instances the symptoms were in part those of meningeal irritation and sometimes simulated the onset of meningitis. Specific meningococcus agglutinins have been demonstrated in the blood serum of vaccinated men as compared with normal controls. Moreover, agglutinins have been demonstrated in the blood serum of chronic carriers of the meningococcus. Evidence is thus brought forward that the relative immunity of chronic carriers to epidemic meningitis may be due to the presence of specific antibodies in the blood stream.

Action of the Extreme Ultraviolet of Tropical Sunlight on the Complementing Power of Serum.—Bovie (*Jour. Med.*, July, 1918) states that the protection which the photosensitive components of the protoplasm enjoy because of the red color of the blood is undoubtedly of very great biological importance. Notwithstanding the obviously painful nature of this relation, teleologism may be avoided by saying that the blood, since it is red, *i. e.*, highly absorbing at the more refrangible end of the spectrum, does protect our bodies from the actinic solar rays (at least in the absence of optical sensitization) quite as efficiently as we protect our photographic plates by using a ruby light. Whether any more useful purpose is served by the red color of our blood is yet to be determined. If the red cells are to be an efficient protection against the actinic rays of the sun it is essential that they be composed of substances possessing considerable photostability. Experiments reported by Dr. A. W. Sellards show this to be the case. The protection which may be offered by the pigments of the skin have not been discussed in this paper, because the experiments have not been carried on in such a manner as to obtain data concerning this phase of the subject.

Protective Therapy for Varicella and a Consideration of its Pathogenesis.—Hess and Unger (*Am. Jour. Dis. of Children*, July, 1918, xvi, 34–38) found it possible to bring about immunity to varicella by means of an intravenous injection of the contents of the vesicles. In thirty-eight instances in which this was carried out it failed to protect in only one case. The authors state that vaccinations of this kind induce neither local nor systemic reaction. The acquisition of immunity likewise indicates that the specific virus is contained in the vesicles. A simpler method of therapy, the application of the lymph to the broken skin or mucous membranes, failed to bring about satisfactory immunity, although it also occasioned no disorder. These investigations have a secondary bearing as to the natural portal of entry of the varicella virus into the body. As the skin and the mucous membranes can be excluded in this connection it would seem most probable that the virus enters by way of the respiratory tract and that contagion comes about through the air. This mode of infection would account for the almost unexampled communicability of this disease.

Scurvy.—(*United States Naval Medical Bulletin*, July, 1918). Extensive outbreaks of scurvy have occurred on land during wars since the Middle Ages; thus 55 out of 143 epidemics analyzed by Hirsch were during hostilities. Three previous endemics in prisoners' camps have

been recorded: (1) 159 cases among 10,000 French prisoners in the Ingoldstadt camp in 1871, (2) among prisoners at Port Blair in the Andaman Islands and (3) among the Hereros in the Southwest African War, the last two being the more serious. In recent wars hygienic measures have prevented scurvy, and only in Russia or countries in which the disease is endemic or sanitary methods are in grave default are large endemics probable. The outbreak among the Austro-German prisoners in Turkestan was much more extensive than in former wars; Disqué saw 504 cases in one military hospital and in a camp of 4000 prisoners there were 754 cases, or 19 per cent. The largest number of cases occurred in March (222) and April (158), when night blindness also increased. The incidence of this large number of cases in the spring was attributed to bad hygienic conditions and the absence of green vegetables in the winter. Giugni observed an outbreak of what appears to have been scurvy among the Italian troops, especially the infantry, at a high elevation in the Dolomite Alps, beginning in June, 1916, increasing during July, reaching its acme in August, declining in October and November and disappearing in the winter. The disease spread in an epidemic fashion to neighboring areas, but not to the same extent as in the original focus, and some sporadic cases were seen at the base. The duration of symptoms ranged from two weeks to two or three months; there were no fatal cases. During a mild epidemic of scurvy among soldiers, Tuchler found that at least 60 per cent. of the patients, including those already ill for three or four weeks, were in an excellent state of nutrition. So far from there being any relation between the severity of the attack and the general state of nutrition, many soldiers in good condition showed the most extensive hemorrhages in the skin and gums. The occurrence of an initial rigor, the continued fever, and the microscopic data led Tuchler to support the view that scurvy is an infective disease, but he does not agree with Much and Baumbach that the infection is conveyed by lice, as all his cases appeared after satisfactory measures for combating this pest had been established. The influence of dark and damp quarters in producing the disease was shown by the cessation of fresh cases when stationary warfare was succeeded by active campaigning in the field and by Weinberger's experience that a regiment provided with a good diet was regularly attacked by scurvy when sent into dark quarters.

Psychiatric Material in the Naval Prison at Portsmouth, N. H.—Jacoby (*United States Naval Medical Bulletin*, July, 1918, No. 3, xii) found among 150 admissions of general court-martial prisoners to the Naval Prison that 66.6 per cent. of the cases fell in psychopathic groups. Attention is called to the fact that 99 of the 150 individuals were in the navy less than one year before they arrived at the prison. In order of frequency the following diagnoses appear: subnormal, 22.6 per cent.; hysteria, 12 per cent.; constitutional inferiority, 6 per cent.; psychopathic personality, 5.3 per cent.; chronic alcoholism, 4 per cent.; dementia precox and cerebrospinal syphilis, each 2 per cent.; manic depressive insanity, anxiety neurosis and epilepsy, each 1.3 per cent. In the 50 cases classed as having no psychiatric condition the cause for commitment to prison was given as "alcohol" in 20 per cent.; a "bad gang" in 14 per cent.; and "women" in 10 per cent. The offences

represented ranged from absence over leave to murder and 56 per cent. of the total offences were of a military nature and not such as would bring the offender into a civil court. He concludes that attention should be directed to the character of the offender as well as to the offence before a man is sent to prison; that the prison population of the navy might be reduced one-half by careful psychiatric examination of each man at the beginning of his naval career and a further reduction of 12.6 per cent. is possible by thorough examination of all offenders before being brought to trial, with the disposition of psychopathic cases through medical channels.

Etiology of Epidemic Poliomyelitis.—TSEN (*Jour. Exper. Med.*, September, 1918) has isolated streptococci from the central nervous system of monkeys dead of poliomyelitis and also from the central nervous system of monkeys dead of other causes, as well as from the brains of normal rabbits. He states that streptococci isolated from poliomyelitic monkeys do not differ from those isolated from monkeys and rabbits dead from other causes. An etiological relation has not been established between streptococci and poliomyelitis. At several times an organism has been isolated that was similar to the globoid bodies culturally, morphologically, and in straining reaction, but the author has not been able to carry it along for more than three generations. The pathogenicity of these organisms has therefore not been tested on monkeys. He has not been able to produce typical lesions of poliomyelitis in rabbits by the injection of either the poliomyelitic virus or streptococci.

Experimental Test of Nuzum's Antipoliomyelitic Serum.—AMOS and EBERSON (*Jour. Exp. Med.*, September, 1918) state that the antistreptococcic serum of Nuzum and Willy has failed to show in the monkey neutralizing or therapeutic power when applied by their methods against small doses of the virus of poliomyelitis. Under the same conditions the serum of monkeys recovered from experimental poliomyelitis proved neutralizing and protective. The experimental and other evidence adduced by those who regard the streptococcus as playing an essential part in the pathology of epidemic poliomyelitis and the antistreptococcic sera as exhibiting therapeutic properties for man and monkeys is regarded as imperfect and inconclusive.

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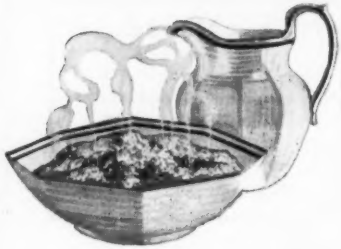

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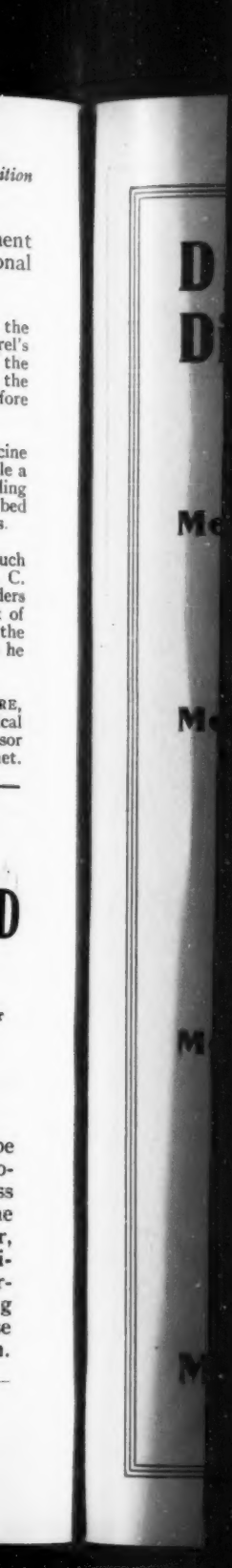

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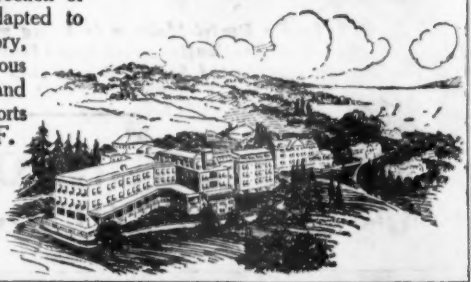

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